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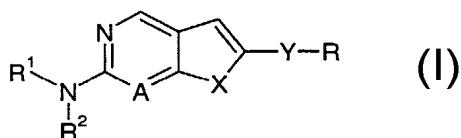
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(54) Title: BICYCLIC PYRIDINE AND PYRIMIDINE P38 KINASE INHIBITORS



(57) Abstract: The present invention discloses compounds correspond-
ing to formula (I), wherein A, R, X, Y, R, R¹ and R² are as defined, phar-
maceutical formulations, methods of making and uses thereof in the treat-
ment of p38 kinase mediated diseases.



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BICYCLIC PYRIDINE AND PYRIMIDINE P38 KINASE INHIBITORS

The present invention relates to certain bicyclic pyridine and pyrimidine derivatives as p38 protein kinase ("p38") inhibitors. In particular, the present invention relates to 2-substituted amino-bicyclic pyridine and pyrimidine compounds, a process for their manufacture, pharmaceutical preparations comprising the same, and methods for using the same.

Mitogen-activated protein kinases (MAP) is a family of proline-directed serine/threonine kinases that activate their substrates by dual phosphorylation. The kinases are activated by a variety of signals including nutritional and osmotic stress, UV light, growth factors, endotoxin and inflammatory cytokines. One group of MAP kinases is the p38 kinase group which includes various isoforms (*e.g.*, p38 α , p39 β , p38 γ and p38 δ). The p38 kinases are responsible for phosphorylating and activating transcription factors as well as other kinases, and are themselves activated by physical and chemical stress, pro-inflammatory cytokines and bacterial lipopolysaccharide.

More importantly, the products of the p38 phosphorylation have been shown to mediate the production of inflammatory cytokines, including TNF, IL-1 and IL-6, and cyclooxygenase-2. Each of these cytokines has been implicated in numerous disease states and conditions. For example, TNF- α is a cytokine produced primarily by activated monocytes and macrophages. Its excessive or unregulated production has been implicated as playing a causative role in the pathogenesis of rheumatoid arthritis. More recently, inhibition of TNF production has been shown to have broad application in the treatment of inflammation, inflammatory bowel disease, Alzheimer's disease, Crohn's disease, multiple sclerosis and asthma.

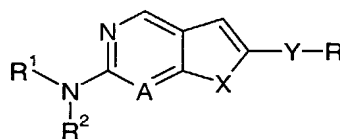
TNF has also been implicated in viral infections, such as HIV, influenza virus, and herpes virus including herpes simplex virus type-1 (HSV-1), herpes

simplex virus type-2 (HSV-2), cytomegalovirus (CMV), varicella-zoster virus (VZV), Epstein-Barr virus, human herpes virus-6 (HHV-6), human herpesvirus-7 (HHV-7), human herpesvirus-8 (HHV-8), pseudorabies and rhinotracheitis, among others.

Similarly, IL-1 is produced by activated monocytes and macrophages, and plays a role in many pathophysiological responses including rheumatoid arthritis, fever and reduction of bone resorption.

The inhibition of these cytokines by inhibition of the p38 kinase is of benefit in controlling, reducing and alleviating many of these disease states.

In one aspect (i) the present invention provides compounds represented by the formula:



I

wherein:

A is N or CH;

R¹ is hydrogen, alkyl or aralkyl;

R² is alkyl, hydroxyalkyl, (R'')₂NCO-alkylene- (where each R'' is independently hydrogen or alkyl), cycloalkyl, heterocyclyl, aryl, heteroaryl or heteroalkyl;

X is O, N(R³) or S, wherein R³ is a hydrogen, alkyl or aryl;

Y is a bond, O, N(R'), C(=O), CH(OR'), CHR', or S(O)_n, wherein n is 0, 1, or 2; and R' is hydrogen or alkyl; and

R is aryl or heteroaryl; and

isomers, pharmaceutically acceptable salts, esters or prodrugs thereof.

In case A is CH it is evident for the person skilled in the art that then the adjacent double bond becomes a single bond.

Further aspects of the present invention are

(ii) The compound according to (i) wherein all substituents have the same meaning as defined in (i) except for R^2 not being heteroalkyl.

(iii) The compound according to (i) wherein:

A is N or CH;

R^1 is hydrogen, alkyl or arylalkyl;

R^2 is alkyl, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl;

X is O, NR^3 or S, wherein R^3 is hydrogen or methyl; and

Y is O, NR' , C(=O), CH(OR'), CH(R'), or $S(O)_n$, wherein n is 0, 1, or 2;

and R' is hydrogen or alkyl; and

R is aryl or heteroaryl.

(iv) The compound according to any one of (i) to (iii) wherein:

A is N;

R^1 is hydrogen;

R^2 is hydroxyalkyl, cycloalkyl, heterocyclyl, aryl or heteroalkyl;

X is O, NR^3 or S, wherein R^3 is alkyl or aryl; and

Y is a bond, O, C(=O), CH(OR'), CH(R'), or S and R' is hydrogen; and

R is aryl.

(v) The compound according to any one of (i) - (iv), wherein:

Y is CH_2 or C(=O); and R is optionally substituted phenyl.

(vi) The compound according to any one of (i) - (v), wherein A is N.

(vii) The compound according any one of (i) - (vi), wherein X is S.

(viii) The compound according to any one of (i) - (vii), wherein R is phenyl which is optionally substituted with alkyl, hydroxyalkyl, halo, trifluoromethyl, alkoxy, trifluoromethoxy, cyano, nitro or amino.

(ix) The compound according to any one of (i) - (viii), wherein Y is C(=O).

5 (x) The compound according to any one of (i) - (ix), wherein R¹ is a hydrogen.

(xi) The compound according to any one of (i) - (x), wherein R² is selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl.

10 (xii) The compound according to any one of (i) - (xi), wherein R² is heterocyclyl.

(xiii) The compound according to any one of (i) - (iv), wherein Y is O or S.

15 (xiv) The compound according to (xiii), wherein A is N.

(xv) The compound according to (xiii) or (xiv), wherein X is S.

20 (xvi) The compound according to any one of (xiii) - (xv), wherein R² is heterocyclyl.

(xvii) The compound according to any one of (xiii) - (xvi), wherein R is aryl.

25 (xviii) The compound according to any one of (xiii) - (xvii), wherein R is optionally substituted phenyl.

30 (xix) The compound according to any one of (xiii) - (xviii), wherein R¹ is hydrogen.

(xx) The compound according to any one of (i), (ii) or (iv), wherein Y is a bond.

(xxi) The compound according to (xx), wherein X is O or NR³.

(xxii) The compound according to (xx) or (xxi), wherein R² is heterocyclyl or aryl.

(xxiii) The compound according to any one of (xx) to (xxiii), wherein R³ is phenyl.

(xxiv) The compound according to (i) to (iv), wherein R is aryl.

(xxv) The compound according to (xxiv), wherein R is optionally substituted phenyl.

(xxvi) The compound according to (xxiv) or (xxv), wherein A is N.

(xxvii) The compound according to any one of (xxiv) - (xxvi), wherein R¹ is hydrogen.

(xxviii) The compound according to any one of (xxiv) - (xxvii), wherein R² is alkyl, hydroxyalkyl, cycloalkyl, heterocyclyl or aryl.

(xxix) The compound according to any one of (xxiv) - (xxvii), wherein R³ is methyl or phenyl.

(xxx) The compound according to any one of (i) to (iv), wherein A is N.

(xxxi) The compound according to (xxx), wherein R is aryl.

(xxxii) The compound according to (xxx) or (xxxi), wherein R^2 is alkyl, hydroxyalkyl, cycloalkyl, heterocyclyl or aryl.

5 (xxxiii) The compound according to any one of (xxx) - (xxxii), wherein R^1 is hydrogen.

(xxxiv) The compound according to any one of (i) to (iii), wherein R is thiophene.

10 (xxxv) The compound according to any one of (i) to (iii), wherein:
 R^1 is hydrogen, R^2 is 4-hydroxycyclohexyl, A is N, X is S, Y is C(=O), and R is phenyl;
 R^1 is hydrogen, R^2 is 4-(N-methylsulfonylpiperidinyl), A is N, X is S, Y is C(=O), and R is phenyl;
15 R^1 is hydrogen, R^2 is 4-tetrahydropyranyl, A is N, X is S, Y is C(=O), and R is phenyl;
 R^1 is hydrogen, R^2 is 4-tetrahydropyranyl, A is N, X is S, Y is C(=O), and R is 4-fluorophenyl;
 R^1 is hydrogen, R^2 is 4-tetrahydropyranyl, A is N, X is S, Y is C(=O), and R is 2-chlorophenyl;
20 R^1 is hydrogen, R^2 is 4-(N-methylsulfonylpiperidinyl), A is N, X is S, Y is C(=O), and R is 2-fluorophenyl;
 R^1 is hydrogen, R^2 is 4-(N-methylsulfonylpiperidinyl), A is N, X is S, Y is C(=O), and R is 3-fluorophenyl;
25 R^1 is hydrogen, R^2 is 4-tetrahydropyranyl, A is N, X is S, Y is C(=O), and R is 3-fluorophenyl;
 R^1 is hydrogen, R^2 is 4-tetrahydropyranyl, A is N, X is S, Y is C(=O), and R is 2-fluorophenyl;
 R^1 is hydrogen, R^2 is 1-(1,1-dimethyl-2-hydroxy)ethyl, A is N, X is S, Y is C(=O), and R is 2-fluorophenyl;
30

R¹ is hydrogen, R² is 4-tetrahydropyranyl, A is N, X is S, Y is C(=O), and R is 4-chlorophenyl;

R¹ is hydrogen, R² is 4-(N-methylsulfonylpiperidinyl), A is N, X is S, Y is C(=O), and R is 4-fluorophenyl;

5 R¹ is hydrogen, R² is 4-(N-methylsulfonylpiperidinyl), A is N, X is S, Y is C(=O), and R is 4-chlorophenyl;

R¹ is hydrogen, R² is 4-(N-methylsulfonylpiperidinyl), A is N, X is S, Y is C(=O), and R is 2-chlorophenyl;

10 R¹ is hydrogen, R² is 4-tetrahydro-1,1-dioxide-2-H-thiopyranyl, A is N, X is S, Y is C(=O), and R is 2-fluorophenyl;

R¹ is hydrogen, R² is 4-tetrahydro-1,1-dioxide-2-H-thiopyranyl, A is N, X is S, Y is C(=O), and R is 3-fluorophenyl;

R¹ is hydrogen, R² is 1-(1,1-dimethyl-2-hydroxy)ethyl, A is N, X is S, Y is C(=O), and R is 3-fluorophenyl;

15 R¹ is hydrogen, R² is 1-(1-methyl-2-methoxy)ethyl, A is N, X is S, Y is C(=O), and R is 3-fluorophenyl;

R¹ is hydrogen, R² is 1-(1-methyl-2-hydroxy)ethyl, A is N, X is S, Y is C(=O), and R is 3-fluorophenyl;

20 R¹ is hydrogen, R² is 1-(1-methyl-2,2-dimethyl-2-hydroxy)ethyl, A is N, X is S, Y is C(=O), and R is 2-chlorophenyl;

R¹ is hydrogen, R² is 1-(1-methyl-2,2-dimethyl-2-hydroxy)ethyl, A is N, X is S, Y is C(=O), and R is 2-fluorophenyl;

R¹ is hydrogen, R² is 4-(N-methylsulfonylpiperidinyl), R' is hydrogen, A is N, X is S, Y is CHR', and R is phenyl;

25 R¹ is hydrogen, R² is 4-(N-methylsulfonylpiperidinyl), R' is hydrogen, A is N, X is S, Y is CH(OR'), and R is phenyl;

R¹ is hydrogen, R² is 4-tetrahydropyranyl, R' is hydrogen, A is N, X is S, Y is CH(OR'), and R is 2-fluorophenyl;

30 R¹ is hydrogen, R² is 4-tetrahydropyranyl, R' is hydrogen, A is N, X is S, Y is CHR', and R is 2-fluorophenyl;

R^1 is hydrogen, R^2 is 4-tetrahydropyranyl, A is N, X is S, Y is C(=O), and R is 2-methylphenyl;

R^1 is hydrogen, R^2 is 4-tetrahydropyranyl, A is N, X is S, Y is C(=O), and R is 2-methoxyphenyl;

5 R^1 is hydrogen, R^2 is 4-tetrahydropyranyl, A is N, X is S, Y is C(=O), and R is 3-methoxyphenyl;

R^1 is hydrogen, R^2 is 4-tetrahydropyranyl, R' is hydrogen, A is N, X is O, Y is CHR', and R is phenyl;

10 R^1 is hydrogen, R^2 is cyclopentyl, R' is hydrogen, A is N, X is O, Y is CHR', and R is phenyl;

R^1 is hydrogen, R^2 is 4-hydroxycyclohexyl, R' is hydrogen, A is NR^3 , X is O, Y is CHR', and R is phenyl;

15 R^1 is hydrogen, R^2 isopropyl, R' is hydrogen, A is N, X is O, Y is CHR', and R is phenyl;

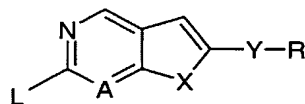
R^1 is hydrogen, R^2 is 4-tetrahydropyranyl, A is N, X is NR^3 , R^3 is methyl, Y is C(=O), and R is 2-methoxyphenyl;

R^1 is hydrogen, R^2 is cyclopentyl, R' is hydrogen, A is N, X is NR^3 , R^3 is methyl, Y is CHR', and R is phenyl;

20 R^1 is hydrogen, R^2 is 4-hydroxycyclohexyl, R' is hydrogen, A is NR^3 , X is N, R^3 is methyl, Y is CHR', and R is phenyl; or

R^1 is hydrogen, R^2 is 4-tetrahydropyranyl, R' is hydrogen, A is N, X is NR^3 , R^3 is methyl, Y is CHR', and R is phenyl.

25 (xxxvi) A compound represented by Formula V:



Formula V

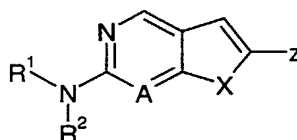
wherein:

30 A is N or CH;

X is O, NR^3 or S, wherein R^3 is hydrogen, alkyl or aryl; and
 Y is a bond, O, NR' , $\text{C}(=\text{O})$, $\text{CH}(\text{OR}')$, $\text{CH}(\text{R}')$, or $\text{S}(\text{O})_n$, wherein n is 0, 1,
 or 2; and R' is hydrogen or alkyl;
 R is aryl or heteroaryl; and
 5 L is $\text{R}^a\text{-S}(\text{O})_{n1}$, where R^a is alkyl or aryl and n1 is 0, 1 or 2.

(xxxvii) The compound of (xxxvi), wherein n1 is 2.

(xxxviii) A compound of Formula VI



Formula VI

wherein:

A is N or CH;

R^1 is hydrogen, alkyl or arylalkyl;

15 R^2 is alkyl, hydroxyalkyl, heteroalkyl, $(\text{R}'')_2\text{NCO-alkylene-}$ (where each R'' is independently hydrogen or alkyl), cycloalkyl, heterocyclyl, aryl, or heteroaryl;

X is O, NR^3 or S, wherein R^3 is hydrogen, alkyl or aryl; and

Z is hydrogen or halo.

(xxxix) The compound of (xxxvii) or (xxxviii) wherein A is N and X is S.

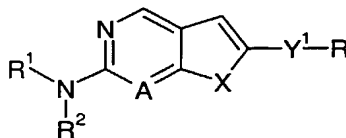
(xxxx) The compound of (xxxviii), wherein:

R^1 is hydrogen; and

25 R^2 is alkyl, hydroxyalkyl, cycloalkyl, heterocyclyl or aryl.

(xxxxi) A pharmaceutical composition comprising a therapeutically effective amount of one or more compound(s) according to any one of (i) to (xxxv) in combination with a pharmaceutically acceptable carrier.

(xxxxii) A process for producing a compound of the formula:



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5 wherein

A is N or CH;

R is aryl or heteroaryl;

R¹ is hydrogen, alkyl or arylalkyl;

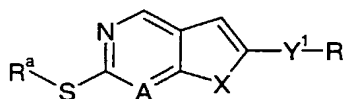
10 R² is alkyl, heteroalkyl, hydroxyalkyl, (R'')₂NCO-alkylene- (where each R'' is independently hydrogen or alkyl), cycloalkyl, heterocyclyl, aryl, or heteroaryl;

X is O, NR³ or S, wherein R³ is hydrogen, alkyl or aryl; and

Y¹ is C(=O), CH(OR'), or CH(R'), wherein R' is hydrogen or alkyl,

said process comprising:

15 a) contacting a thioether of the formula:

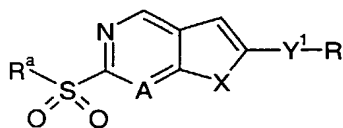


wherein

20 A, R, X and Y¹ are as defined above; and

R^a is alkyl or aryl,

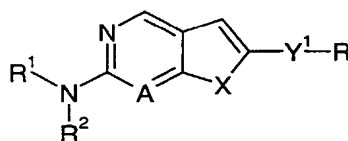
with an oxidizing agent to produce an alkylsulfone compound of the formula:



25 and

b) contacting the alkylsulfone compound with an amine compound of the formula NHR^1R^2 , wherein R^1 and R^2 are as defined above to produce the compound of Formula IA.

5 (xxxxiii) A process of producing a compound of Formula IB:



IB

wherein

A is N or CH;

10 R is aryl or heteroaryl;

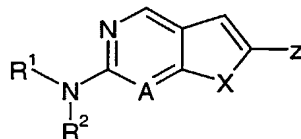
R^1 is hydrogen, alkyl or arylalkyl;

R^2 is alkyl, heteroalkyl, hydroxyalkyl, $(\text{R}'')_2\text{NCO-alkylene-}$ (where each R'' is independently hydrogen or alkyl), cycloalkyl, heterocyclyl, aryl, or heteroaryl;

15 X is O, NR^3 or S, wherein R^3 is hydrogen, alkyl or aryl; and

Y^1 is O, NR' , or S(O)_n , wherein n is 0, 1, or 2; and R' is hydrogen or alkyl;

said process comprising contacting a compound of the formula:



wherein

20 A, X, R^1 and R^2 are as defined above; and

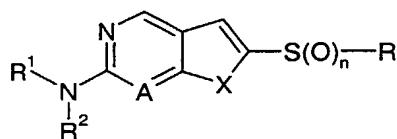
Z is halide,

with an aromatic or heteroaromatic compound of the formula $\text{HY}^1\text{-R}$, optionally in the presence of a base, to produce the compound of Formula IB, where Y^1 is O, NR' , or S,

25 and when Y^1 is S, said process further comprising:

contacting the compound of Formula IB, where Y^1 is S with an oxidizing agent to produce the compound of Formula IB, where Y^1 is $S(O)_n$, where n is 1 or 2.

5 (xxxxiv) A process of producing a compound of Formula IC:



IC

wherein

n is 0, 1 or 2;

10 A is N or CH;

R is aryl or heteroaryl;

R^1 is hydrogen, alkyl or arylalkyl;

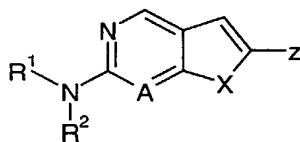
R^2 is alkyl, heteroalkyl, hydroxyalkyl, $(R'')_2NCO$ -alkylene- (where each R'' is independently hydrogen or alkyl), cycloalkyl, heterocyclyl, aryl, or

15 heteroaryl; and

X is O, NR^3 or S, wherein R^3 is hydrogen, alkyl or aryl;

said process comprising:

(a) contacting a compound of the formula:



20 wherein

R^1 , R^2 , A and X are as defined above; and

Z is halide,

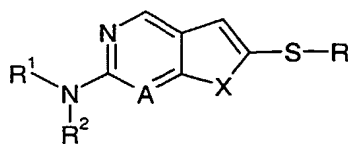
with an organometallic reagent; and

(b) adding an aryl or heteroaryl disulfide of the formula:

25 $R-S-S-R$

to produce a thioether compound of the formula:

13



and when n is 1 or 2, said process further comprising:

(c) contacting the thioether compound with an oxidizing agent to produce the compound of Formula IC where n is 1 or 2.

5

(xxxxv) A process as claimed in any one of (xxxix) to (xxxiv) wherein X is methyl or phenyl and R² is not heteroalkyl.

10

(xxxxvi) A compounds as claimed in any one of (i) to (xxxv) whenever prepared by a process as claimed in any one of (xxxix) to (xxxiv).

15

(xxxxvii) A method for treating a p38 protein kinase mediated disorder comprising administering to a patient in need of such treatment, an effective amount of a compound according to any one of (i) to (xxxv).

20

(xxxxviii) The method of (xxxxvii), wherein the p38 protein kinase mediated disorder is selected from the group consisting of arthritis, Crohn's disease, Alzheimer's disease, irritable bowl syndrome, adult respiratory distredd syndrome, and chronic obstructive pulmonary disease.

25

(xxxxix) Use of a compound as claimed in any one of (i) to (xxxv) for the preparation of a medicament for the treatment of a p38 protein kinase mediated disorder.

(v) The use of (xxxxix), wherein the p38 protein kinase mediated disorder is selected from the group consisting of arthritis, Crohn's disease, Alzheimer's disease, irritable bowl syndrome, adult respiratory distredd syndrome, and chronic obstructive pulmonary disease.

The compounds of formula I and their aforementioned salts are inhibitors of protein kinases, and exhibit effective activity against p38 *in vivo*. Therefore, the compounds can be used for the treatment of diseases mediated by the pro-inflammatory cytokines such as TNF and IL-1.

5 Thus, in another aspect, the present invention relates to methods for the treatment of p38 mediated diseases or conditions in which a therapeutically effective amount of a compound of formula I is administered to a patient in need of such treatment.

10 In yet another aspect, the present invention relates to methods for preparing the compounds described above.

 In yet still another aspect, the present invention relates to methods for preparing medicaments useful for the treatment of the p38 mediated diseases and conditions.

15 As used herein, the term "alkyl" means a linear or branched saturated monovalent hydrocarbon moiety of one to six carbon atoms, e.g., methyl, ethyl, *n*-propyl, 2-propyl, *tert*-butyl, pentyl, and the like.

 "Alkylene" means a linear or branched saturated divalent hydrocarbon moiety of one to six carbon atoms, e.g., methylene, ethylene, propylene, and the like.

20 The term "aryl" refers to a monovalent monocyclic or bicyclic aromatic hydrocarbon moiety which is optionally substituted independently with one or more, preferably one, two or three, substituents. Preferably, each substituent is independently selected from the group consisting of alkyl, haloalkyl, halo, hydroxy, amino, haloalkoxy, heteroalkyl, methylenedioxy, ethylenedioxy, -Y-aryl, -Y-heteroaryl, -Y-cycloalkyl, -Y-heterocyclyl, -Y-OR^P, -Y-NR^PR^Q, -Y-C(O)-R^P, -YS(O)₀₋₂R^P, -Y-N-S(O)₂R^P, -Y-S(O)₂NR^PR^Q, -Y-N-C(O)NR^PR^Q, where Y is absent
25 or a C₁-C₃ alkylene group, and R^P and R^Q are independently selected from hydrogen, alkyl, haloalkyl, hydroxy, alkoxy, aryl, heteroaryl, cycloalkyl, and heterocyclyl. A particularly preferred group of aryl substituents are those selected from alkyl, haloalkyl, halo, hydroxy, amino, haloalkoxy and heteroalkyl. Further aryl
30 substituents are cyano and nitro. Within this group of aryl substituents, halide, alkyl and alkoxy are especially preferred. More specifically the term aryl includes, but is

not limited to, phenyl, chlorophenyl, methoxyphenyl, 1-naphthyl, 2-naphthyl, and the derivatives thereof.

“Aralkyl” means a moiety of the formula $-R^xR^y$ where R^x is an alkylene group and R^y is an aryl group as defined above. Exemplary aralkyls include benzyl, phenylethylene, and the like.

The term “cycloalkyl” as used herein refers to a saturated monovalent cyclic hydrocarbon moiety of three to seven ring carbons, e.g., cyclopentyl, cyclobutyl, cyclohexyl, and the like. Cycloalkyl may optionally be substituted with one, two or three substituents. Preferably, each substituent is independently selected from the group consisting of alkyl, hydroxy, alkoxy, amino, monosubstituted amino, disubstituted amino, haloalkyl, halo, cyanoalkyl, oxo (i.e., carbonyl oxygen), heteroalkyl, heterocyclyl, hydroxyalkyl, and $-(X)_n-C(O)R'$ (where, X is O or NR”, n is 0 or 1, R” is hydrogen, alkyl, haloalkyl, amino, monosubstituted amino, disubstituted amino, hydroxy, alkoxy, alkyl or optionally substituted phenyl, and R’ is H or alkyl), and $-S(O)_nR'$ (wherein n is 0 to 2). A particularly preferred group of cycloalkyl substituents are those selected from alkyl, hydroxy, alkoxy, amino, monosubstituted amino, disubstituted amino, haloalkyl and halo. Among this group of cycloalkyl substituents, alkyl, hydroxy, alkoxy, haloalkyl and halo are especially preferred with hydroxyl being most preferred. More specifically, the term cycloalkyl includes, cyclopentyl, cyclohexyl, 4-hydroxycyclohexyl, and the like.

The term “halo,” “halide” or “halogen,” when referring to a substituent means fluoro, chloro, bromo, or iodo.

The term “haloalkyl” means alkyl substituted with one or more same or different halo atoms, e.g., $-CH_2Cl$, $-CF_3$, $-CH_2CF_3$, $-CH_2CCl_3$, and the like, and further includes those alkyl groups such as perfluoroalkyl in which all alkyl hydrogen atoms are replaced by fluorine atoms.

The term “heteroalkyl” as used herein means an alkyl moiety defined above, wherein one, two or three hydrogen atoms have been replaced with a substituent independently selected from the group consisting of $-OR^a$, $-NR^bR^c$, and $S(O)_nR^d$ (where n is an integer from 0 to 2), with the understanding that the point of attachment of the heteroalkyl moiety is through a carbon atom, wherein R^a is

hydrogen, acyl, alkyl, cycloalkyl, or cycloalkylalkyl; R^b and R^c are independently of each other hydrogen, acyl, alkyl, cycloalkyl, or cycloalkylalkyl; or R^b and R^c together form cycloalkyl or arylcycloalkyl; and when n is 0, R^d is hydrogen, alkyl, cycloalkyl, or cycloalkylalkyl, and when n is 1 or 2, R^d is alkyl, cycloalkyl, cycloalkylalkyl, amino, acylamino, monoalkylamino, or dialkylamino. Representative examples include, but are not limited to, 2-hydroxyethyl, 3-hydroxypropyl, 2-hydroxy-methylethyl, 2,3-dihydroxypropyl, 1-hydroxymethylethyl, 3-hydroxybutyl, 2,3-dihydroxybutyl, 2-hydroxy-1-methylpropyl, 2-aminoethyl, 3-aminopropyl, 2-methylsulfonylethyl, aminosulfonylmethyl, aminosulfonylethyl, methylamino-sulfonylmethyl, methylaminosulfonylethyl, methylaminosulfonylpropyl, and the like. When R^a in the moiety $-OR^a$ is hydrogen, "heteroalkyl" is also referred to as "hydroxyalkyl" and includes, but is not limited to, 2-hydroxyethyl, 3-hydroxypropyl, 2-hydroxymethylethyl, 2,3-dihydroxypropyl, 1-hydroxymethylethyl, 3-hydroxy-butyl, 2,3-dihydroxybutyl, 2-hydroxy-1-methylpropyl.

"Monosubstituted amino" means a moiety $-NHR^e$ where R^e is alkyl, heteroalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, heteroaralkenyl, heterocyclyl, or heterocyclylalkyl, e.g., methylamino, ethylamino, phenylamine, benzylamine, and the like. Similarly, the term "disubstituted amino" refers to a moiety $-NR^gR^h$ wherein R^g and R^h are, independently of each other, alkyl, heteroalkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, aryl, aralkyl, aralkenyl, heteroaryl, heteroaralkyl, heteroaralkenyl, heterocyclyl, or heterocyclylalkyl, or R^g and R^h together with the nitrogen atom to which they are attached form a heterocyclyl ring. Representative examples include, but are not limited to, dimethylamino, methylethylamino, di(1-methyl-ethyl)amino, piperaziny, piperdiny and the like.

"Heterocyclyl" means a saturated cyclic moiety in which one or two ring atoms are heteroatoms selected from N, O, or $S(O)_n$ (where n is an integer from 0 to 2), the remaining ring atoms being C, where one or two C atoms may optionally contain a carbonyl oxygen group, e.g., one or two atoms in the ring may be a moiety of the formula $-C(=O)-$. The heterocyclyl ring may be optionally substituted independently with one, two, or three substituents selected from alkyl, hydroxy,

hydroxyalkyl, alkoxy, heteroalkyl, and haloalkyl. More specifically the term heterocyclyl includes, but is not limited to, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, and the like.

“Heteroaryl” means a monovalent monocyclic or bicyclic aromatic moiety of 5 to 12 ring atoms containing one, two, or three ring heteroatoms each independently selected from N, O, or S, the remaining ring atoms being C. The heteroaryl ring can optionally be substituted with one or more substituents, preferably one or two substituents, each substituent being independently selected from alkyl, haloalkyl, heteroalkyl, heterocyclyl, halo, nitro, cyano, carboxy, acyl, $-(\text{alkylene})_n\text{-COOR}$ (where n is 0 or 1 and R is hydrogen, alkyl, optionally substituted phenylalkyl, or optionally substituted heteroaralkyl), or $-(\text{alkylene})_n\text{-CONR}^a\text{R}^b$ (where n is 0 or 1, and R^a and R^b are, independently of each other, hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, aryl, or R^a and R^b together with the nitrogen atom to which they are attached form a heterocyclyl ring). More specifically the term heteroaryl includes, but is not limited to, pyridyl, furanyl, thiophenyl, thiazolyl, isothiazolyl, triazolyl, imidazolyl, isoxazolyl, pyrrolyl, pyrazolyl, pyrimidinyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoisothiazolyl, benzotriazolyl, indolyl, isoindolyl, benzoxazolyl, quinolyl, isoquinolyl, benzimidazolyl, benzisoxazolyl, benzothiophenyl, dibenzofuran, and benzodiazepin-2-one-5-yl, and the derivatives thereof. [This list can remain as such.]

The term “acyl” refers to the group $-\text{C}(\text{O})\text{R}^r$ where R^r is alkyl, haloalkyl, heteroalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl.

“Alkoxy”, “aryloxy”, “aralkyloxy”, or “heteroaralkyloxy” means a moiety -OR where R is an alkyl, aryl, aralkyl, or heteroaralkyl, respectively, as defined above e.g., methoxy, phenoxy, pyridin-2-ylmethyloxy, benzyloxy, and the like.

“Leaving group” has the meaning conventionally associated with it in synthetic organic chemistry, i.e., an atom or a group capable of being displaced by a nucleophile and includes halo (such as chloro, bromo, and iodo), alkanesulfonyloxy, arenesulfonyloxy, alkylcarbonyloxy (e.g., acetoxy), arylcarbonyloxy, mesyloxy, tosyloxy, trifluoromethanesulfonyloxy, aryloxy (e.g., 2,4-dinitrophenoxy), methoxy, N,O-dimethylhydroxylamino, and the like.

“Pharmaceutically acceptable excipient” means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipient that is acceptable for veterinary use as well as human pharmaceutical use. A “pharmaceutically acceptable excipient” as used in the specification and claims includes both one and more than one such excipient.

“Pharmaceutically acceptable salt” of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

The terms “pro-drug” and “prodrug” are used interchangeably herein and refer to any compound which releases an active parent drug according to Formula I *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound of Formula I are prepared by modifying one or more functional group(s) present in the compound of Formula I in such a way that the modification(s) may be cleaved *in vivo* to release the parent compound. Prodrugs include compounds of

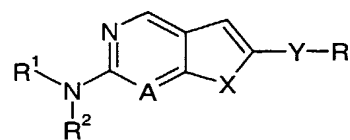
Formula I wherein a hydroxy, amino, or sulfhydryl group in a compound of Formula I is bonded to any group that may be cleaved *in vivo* to regenerate the free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, esters (e.g., acetate, formate, and benzoate derivatives), carbamates (e.g.,
5 N,N-dimethylaminocarbonyl) of hydroxy functional groups in compounds of Formula I, and the like.

“Protecting group” refers to a grouping of atoms that when attached to a reactive group in a molecule masks, reduces or prevents that reactivity. Examples of protecting groups can be found in T.W. Green and P.G. Futs, *Protective Groups in*
10 *Organic Chemistry*, (Wiley, 2nd ed. 1991) and Harrison and Harrison et al., *Compendium of Synthetic Organic Methods*, Vols. 1-8 (John Wiley and Sons, 1971-1996). Representative amino protecting groups include, formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl (CBZ), *tert*-butoxycarbonyl (Boc), trimethyl silyl (TMS), 2-trimethylsilyl-ethanesulfonyl (SES), trityl and substituted
15 trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl (Fmoc), nitro-veratryloxycarbonyl (NVOC), and the like. Representative hydroxy protecting groups include those where the hydroxy group is either acylated or alkylated such as benzyl, and trityl ethers as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers and allyl ethers.

20 “Treating” or “treatment” of a disease includes: (1) preventing the disease, i.e., causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease; (2) inhibiting the disease, i.e., arresting or reducing the development of the disease or its clinical symptoms; or (3) relieving the disease,
25 i.e., causing regression of the disease or its clinical symptoms.

“A therapeutically effective amount” means the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The “therapeutically effective amount” will vary depending on the compound, the disease and its severity and the age, weight, etc., of
30 the mammal to be treated.

In one embodiment, the present invention provides compounds represented by the formula:



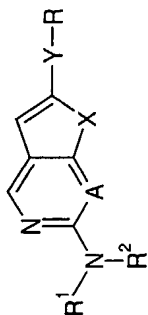
I

5 wherein A, R¹, R², X, Y and R are as defined above.

Some of the representative compounds of formula I are shown in Table 1 below.

Table 1

Compounds of formula I, wherein the values of R¹, R², R³, R', A, X, Y and R are set forth below:

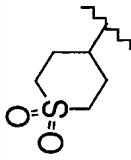


I

Cpd. #	R ¹	R ²	R'	R ³	A	X	Y	R	MP °C	MS M+H
1	H	4-hydroxy-cyclohexyl	-	-	N	S	CO	phenyl	102.6- 103.8	354
2	H	N-methylsulfonylpiperidin-4-yl	-	-	N	S	CO	phenyl	216.3- 217.6	417
3	H	tetrahydropyran-4-yl	-	-	N	S	CO	phenyl	219.5- 220.5	340
4	H	tetrahydropyran-4-yl	-	-	N	S	CO	4-fluorophenyl	236-238.7	358
5	H	tetrahydropyran-4-yl	-	-	N	S	CO	2-chlorophenyl	-	-
6	H	N-methylsulfonylpiperidin-4-yl	-	-	N	S	CO	2-fluorophenyl	213.3- 216.1	435
7	H	N-methylsulfonylpiperidin-4-yl	-	-	N	S	CO	3-fluorophenyl	225.4- 225.7	435

Cpd. #	R ¹	R ²	R'	R ³	A	X	Y	R	MP °C	MS M+H
8	H	tetrahydropyran-4-yl	-	-	N	S	CO	3-fluorophenyl	186.7- 188.8	358
9	H	tetrahydropyran-4-yl	-	-	N	S	CO	2-fluorophenyl	195.2- 195.5	358
10	H	(1,1-dimethyl-2-hydroxy)ethyl	-	-	N	S	CO	2-fluorophenyl	105-108.5	346
11	H	tetrahydropyran-4-yl	-	-	N	S	CO	4-chlorophenyl	261.4- 262.9	374
12	H	N-methylsulfonylpiperidin-4-yl	-	-	N	S	CO	4-fluorophenyl	250.3- 251.1	435
13	H	N-methylsulfonylpiperidin-4-yl	-	-	N	S	CO	4-chlorophenyl	260.8- 261.8	-
14	H	N-methylsulfonylpiperidin-4-yl	-	-	N	S	CO	2-chlorophenyl	188.1- 188.5	451
15	H	1,1-dioxo-tetrahydrothiopyran-4-yl	-	-	N	S	CO	2-fluorophenyl	217.9- 221.8	406
	H	N-methylsulfonylpiperidin-4-yl	-	-	N	S	CO	3-fluorophenyl	191-193.4	406
17	H	(1,1-dimethyl-2-hydroxy)ethyl	-	-	N	S	CO	3-fluorophenyl	133.3- 134.6	346.1
18	H	(1-methyl-2-methoxy)ethyl	-	-	N	S	CO	3-fluorophenyl	159.4-	346

Cpd. #	R ¹	R ²	R'	R ³	A	X	Y	R	MP °C	MS M+H
									167.2	
19	H	(1-methyl-2-hydroxy)ethyl	-	-	N	S	CO	3-fluorophenyl	148.6- 150.5	332
20	H	(1-methyl-2,2-dimethyl-2-hydroxy)ethyl	-	-	N	S	CO	2-chlorophenyl	106-113	376
21	H	1-(2,2-dimethyl-2-hydroxyethyl)ethyl	-	-	N	S	CO	2-fluorophenyl	104.4- 117.3	360
22	H	N-methylsulfonylpiperidin-4-yl	H	-	N	S	CHR'	phenyl	215-217	403
23	H	N-methylsulfonylpiperidin-4-yl	H	-	N	S	CH(OR')	phenyl	152.2- 162.1	419
24	H	tetrahydropyran-4-yl	H	-	N	S	CH(OR')	2-fluorophenyl	-	360.2
25	H	tetrahydropyran-4-yl	H	-	N	S	CHR'	2-fluorophenyl	217-219	344
26	H	tetrahydropyran-4-yl	-	-	N	S	CO	2-methyl-phenyl	183-188	354
27	H	tetrahydropyran-4-yl	-	-	N	S	CO	2-methoxy-phenyl	194.4- 198.4	370
28	H	tetrahydropyran-4-yl	-	-	N	S	CO	3-methoxy-phenyl	206-208.6	370

Cpd. #	R ¹	R ²	R'	R ³	A	X	Y	R	MP °C	MS M+H
29	H	tetrahydropyran-4-yl	H	-	N	O	CHR'	phenyl		310.3
30	H	cyclopentyl	H	-	N	O	CHR'	phenyl	-	294.2
31	H	4-hydroxycyclohexyl	H	-	N	O	CHR'	phenyl	-	324.2
32	H	tetrahydropyran-4-yl	-	methyl	N	NR ³	CO	2-methoxy-phenyl	-	367.2
33	H	cyclopentyl	H	methyl	N	NR ³	CHR'	phenyl	-	307.3
34	H	4-hydroxycyclohexyl	H	methyl	N	NR ³	CHR'	phenyl	-	337.2
36	H	tetrahydropyran-4-yl	H	methyl	N	NR ³	CHR'	phenyl	-	323.2
37	H	 (i.e., 1,1-dioxo-tetrahydrothiopyran-4-yl)	-	-	N	S	CO	4-fluorophenyl	>300	406
37	H	tetrahydropyran-4-yl	-	-	N	O	-	phenyl	224-226	296

Cpd. #	R ¹	R ²	R'	R ³	A	X	Y	R	MP °C	MS M+H
38	H	isopropyl	H	-	N	O	CHR'	phenyl		268.2
39	H	phenyl	-	phenyl	N	NR ³	-	4-methoxyphenyl		
40	H	1-(2-hydroxyethyl)-3-hydroxypropyl	-	-	N	S	CO	2-methoxyphenyl		388
41	H	tetrahydropyran-4-yl	-	-	N	S	S	2,4-difluorophenyl		380
42	H	tetrahydropyran-4-yl	-	-	N	S	O	2,4-difluorophenyl		364
43	H	tetrahydropyran-4-yl	-	-	N	S	S	phenyl		344

In one preferred group of compounds of Formula I, R is aryl. Preferred aryl groups are optionally substituted phenyl. Particularly preferred optionally substituted phenyls are phenyl (i.e., non-substituted phenyl), mono- and di-halo substituted phenyls, alkylsubstituted phenyls, and alkoxysubstituted phenyl.

5 Especially preferred optionally substituted phenyls are phenyl, 4-fluorophenyl, 2-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-chlorophenyl, 2-methoxyphenyl, 2-methylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, and 2,4-difluorophenyl.

In another preferred group of compounds of Formula I, Y is C(=O), CH₂, CH(OH), a bond (i.e., absent), S and O.

10 Yet in another preferred group of compounds of Formula I, A is N.

Still in another preferred group of compounds of Formula I, R¹ is hydrogen.

Yet still in another preferred group of compounds of Formula I, R² is heterocyclyl, preferably heterocyclyl means a saturated N, S (SO or SO₂) or O containing six membered cyclic moiety which is optionally substituted, e.g.

15 alkylsulfonyl, more preferably heterocyclyl means piperidinyl, tetrahydropyranyl or tetrahydrothiopyranyl or 1,1-dioxo-tetrahydrothiopyranyl, furthermore in this preferred group R² is also cycloalkyl, heteroalkyl, preferably heteroalkyl means alkyl as defined herein substituted with one or more, preferably 1 to 4 substituents selected from alkyl, alkoxy or hydroxy, furthermore in this preferred group R² is also alkyl, and aryl, 20 preferably phenyl. Within this group of R² is 4-hydroxycyclohexyl, N-methylsulfonylpiperidin-4-yl, tetrahydropyran-4-yl, (1,1-dimethyl-2-hydroxy)ethyl, 1,1-dioxo-tetrahydrothiopyran-4-yl, 2-methoxy-1-methylethyl, 2-hydroxy-1-methylethyl, 1,2-dimethyl-2-hydroxypropyl, cyclopentyl, isopropyl, phenyl, and 1-(2-hydroxyethyl)-3-hydroxypropyl. Furthermore R² is (1-methyl-2,2-dimethyl-2-hydroxy)ethyl or 25 1-(2,2-dimethyl-2-hydroxyethyl)ethyl.

In another preferred group of compounds of Formula I, X is O, S or NR³ with R³ preferably alkyl or aryl and aryl is preferably phenyl.

Still further, combinations of the preferred groups described herein form other preferred embodiments. In this manner, a variety of preferred compounds are 30 embodied within the present invention. Representative groups of particularly preferred compounds are described below.

One preferred group of compounds of formula I are those wherein Y is CH₂ or C(=O); and R is a phenyl optionally substituted with a halogen, methyl, trifluoromethyl, alkoxy, trifluoromethoxy, cyano, nitro or amino.

5 More preferred compounds in this embodiment are compounds of formula I, wherein A is N, Y is CH₂ or C(=O), X is S. Still more preferred compounds are compounds of formula I wherein A is N, Y is C(=O), R¹ is hydrogen and R² is a cycloalkyl, heterocycloalkyl or an aryl.

10 Particularly preferred compounds of formula I are those wherein A is N, X is S, Y is C(=O) and R is a phenyl optionally substituted with halogen, alkyl, trifluoromethyl, alkoxy and hydroxyalkyl, R¹ is hydrogen and R² is a cycloalkyl, heterocycloalkyl or an aryl.

Most preferred compounds are those of formula I wherein A is N, X is S, Y is C(=O), R is a phenyl substituted with halogen, alkyl, trifluoromethyl, alkoxy and hydroxyalkyl, R¹ is hydrogen and R² is a heterocyclyl group.

15 In another preferred embodiment of compounds of Formula I, Y is O or S. Within this group of compounds of Formula I, preferably A is N. More preferred compounds within this group are those where X is S. In particular, compounds where R² is heterocyclyl are still more preferred. Still further preferred group of compounds within this group are those where R is aryl, in particular where R is optionally substituted phenyl. More particularly, those compounds where R¹ is hydrogen are especially preferred.

20 Still in another preferred embodiment of compounds of Formula I, Y is a bond, i.e., R is directly attached to the core heteroaryl group on the carbon atom adjacent to the X moiety. A particularly preferred groups of compounds within this embodiment are those where X is O or NR³. Still more preferred are those where R² is heterocyclyl or aryl. One specific group of compounds within this group are those where R³ is phenyl.

25 Yet in another preferred embodiment of compounds of Formula I, R is aryl, preferably optionally substituted phenyl. Particularly preferred are those where A is N. More preferred compounds within this group of compounds of Formula I are those where R¹ is hydrogen. Still more preferred group of compounds are those

30

where R^2 is alkyl, hydroxyalkyl, cycloalkyl, heterocyclyl or aryl, with those where R^3 is methyl or phenyl being especially preferred.

In yet another preferred embodiment of compounds of Formula I, A is N. Preferred compounds within this group are those where R is aryl, with compounds
5 where R^2 is alkyl, hydroxyalkyl, cycloalkyl, heterocyclyl or aryl being particularly preferred. Especially preferred are those where R^1 is hydrogen.

The compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms and are intended to be encompassed within the scope of the invention. Furthermore, as stated above, the present
10 invention also includes all pharmaceutically acceptable salts of the compounds along with prodrug forms of the compounds and all stereoisomers whether in a pure chiral form, a racemic mixture, or enantiomeric mixture forms.

The compounds of formula I are capable of further forming pharmaceutically acceptable acid addition salts. As stated above, all of these forms are also
15 contemplated within the scope of the claimed invention.

Pharmaceutically acceptable addition salts of the compounds of formula I include salts derived from inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, phosphorus, and the like, as well as the salts derived from organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-
20 substituted alkanolic acids, hydroxy alkanolic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate,
25 dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartarate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate (see, or example, Berge et al., "Pharmaceutical Salts," *J. of Pharmaceutical Science*, 1977,
30 66, 1-19).

The acid addition salts of the basic compounds can be prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. The free base form can be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms may differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base for the purposes of the present invention.

Pharmaceutically acceptable base addition salts can be formed with metal ions or amines, such as alkali and alkaline earth metal ions or organic amines. Examples of metal ions which are used as cations include sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are N, N'-dibenzylethylenediamine, chlororocaine, choline, diethanolamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge et al., *supra*).

The base addition salts of acidic compounds can be prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form can be regenerated by contacting the salt form with an acid and isolating the free acid in the conventional manner. The free acid forms may differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid for the purposes of the present invention.

The compounds of the present invention can be prepared by a variety of methods, using procedures well-known to those of skill in the art. The following schemes illustrate the processes of making the compounds of the invention. The abbreviations used herein have the following meaning:

MCPBA: m-chloroperbenzoic acid.

NMP: N-methylpyrrolidine.

THF: tetrahydrofuran.

TLC: thin layer chromatography.

EtOAc: ethyl acetate.

Scheme 1 describes the method of preparing a compound of formula I(a) and its analogs I(b) and I(c).

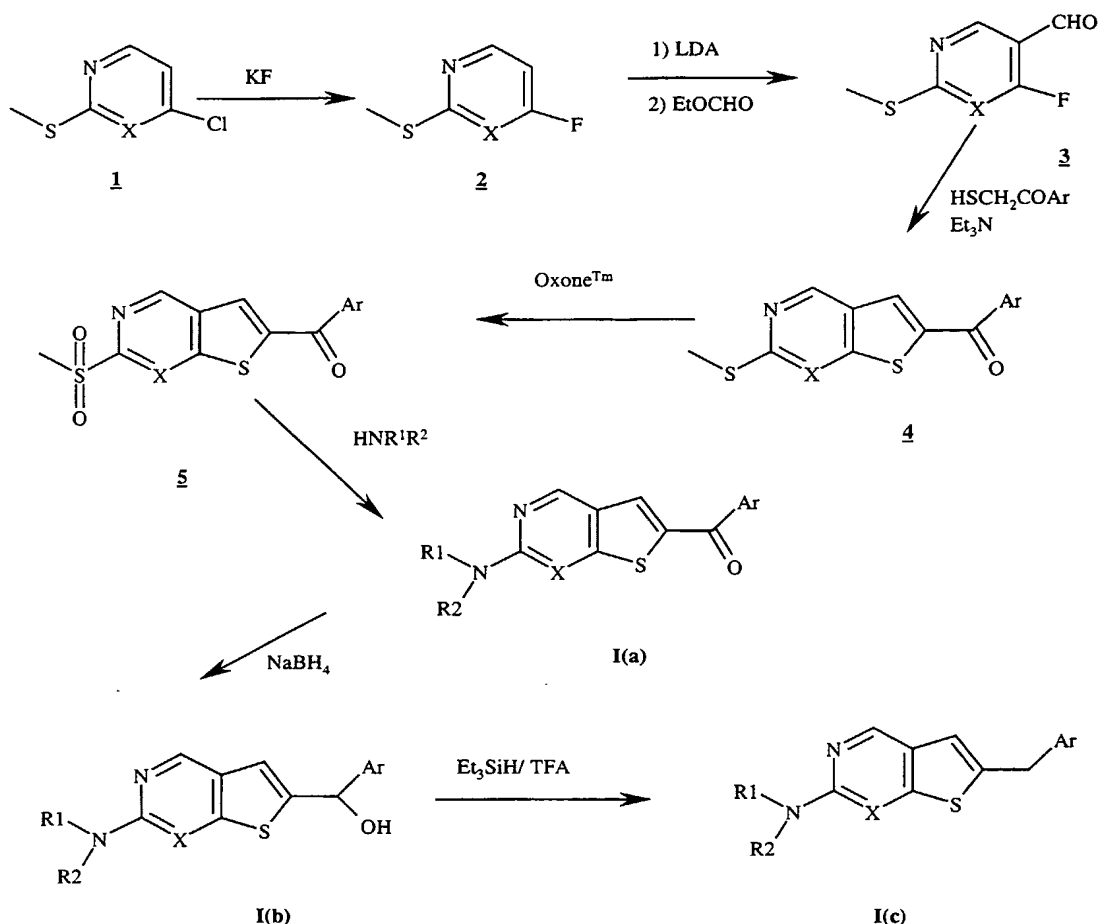
Treatment of a compound of formula 1 with potassium fluoride provides a compound of formula 2, which is then converted to a carboxaldehyde 3 according to the literature procedure (Ple, N.; Turck, A.; Heynderickx, A.; Queguiner, G. J.; *Heterocyclic Chem.* 1994, 31, 1311). Carboxaldehyde 3 can be coupled with the substituted phenacylthiols without further purification to give a compound of formula 4. The reaction is typically carried out with triethylamine as the base at about 0 °C to about room temperature.

Oxidation of compound 4 with an oxidizing agent, such as 3-chloroperbenzoic acid (i.e., MCPBA) or Oxone[®], provides a sulfone 5 which can be converted into a variety of target compounds. Typically the oxidation of 5 is carried out in a solvent which is inert under the conditions of the oxidation. For example, when MCPBA is used as the oxidizing agent, the solvent is preferably a halogenated aliphatic hydrocarbon, especially dichloromethane.

When Oxone[®] is used as the oxidizing agent, the solvent is typically a mixture of water and tetrahydrofuran. The reaction temperature depends on the solvent used. For an organic solvent, the reaction temperature is generally at about -20 °C to about 50 °C, preferably about 0 °C to about room temperature. When water is used as the solvent, the reaction temperature is generally from about 0 °C to about 50 °C, preferably about 0 °C to about room temperature.

Reaction of compound 5 with an amine of formula R¹R²NH, where R¹ and R² are as defined above, affords a compound of formula I(a). The reaction can be carried out in the presence or absence of a solvent. Conveniently, the reaction is carried out at temperatures of from about 0 °C to about 200 °C, more preferably about room temperature to about 150 °C.

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Scheme 1

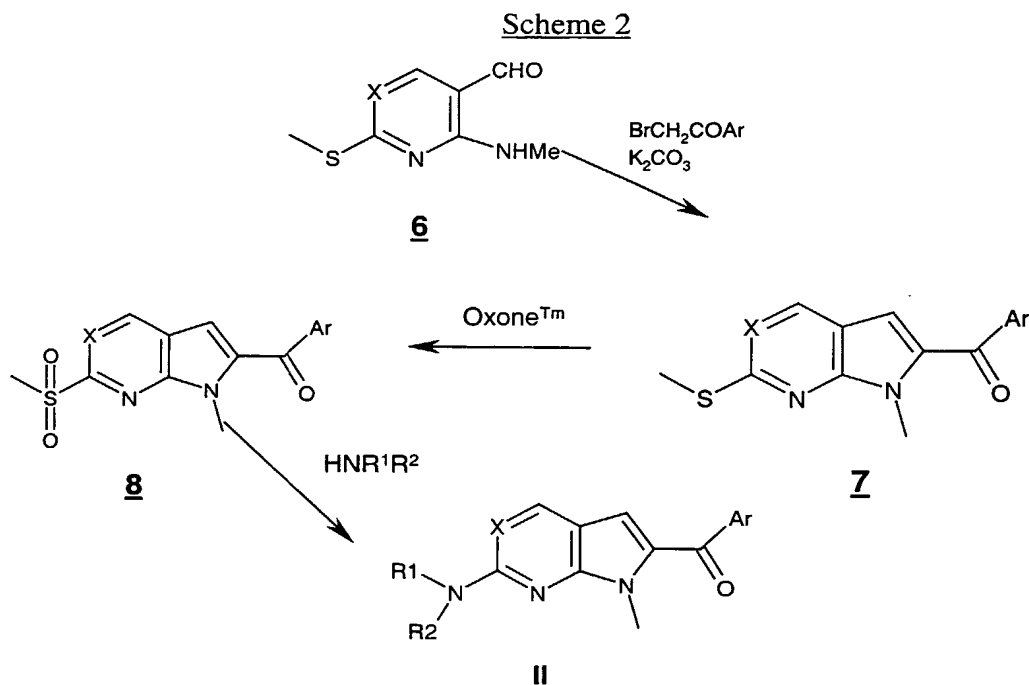
Compound I(a) can be reduced to the alcohol of formula I(b) by carrying out the reduction with a reducing agent, such as sodium borohydride in ethanol at room temperature. Compound of formula I(b) can in turn be converted to a compound of formula I(c). This reduction is usually carried out in dichloromethane with triethylsilane and trifluoroacetic acid.

Alternatively (not shown here), reaction of compound 5 with ammonia provides a compound of formula I(a)' (i.e., compound of formula I, where R^1 and R^2 are hydrogen). Further alkylation of I(a)' then provides compounds of formula I, where R^1 and/or R^2 are not hydrogen. The reaction can be carried out in the presence or absence of solvent. Conveniently, the reaction is carried out at temperatures of from about 0°C to about 200°C , more preferably about room temperature to about 150°C . Alternatively (not shown here), in some cases rather than using the sulfone

5, the sulfide 4 can be reacted directly with an amine (R^1R^2NH) to provide the compounds of formula I(a).

Scheme 2 illustrates a method of preparing the pyrrole analog of compound I(a). The condensation of the amino aldehyde 6 with a substituted phenacyl bromide gives compound 7. The reaction is typically carried out in NMP at 80 °C. Compound 7 is then oxidized to sulfone 8 by method described above under Scheme 1. Sulfone 8 is then reacted with an appropriate amine as described above to afford compound of formula II.

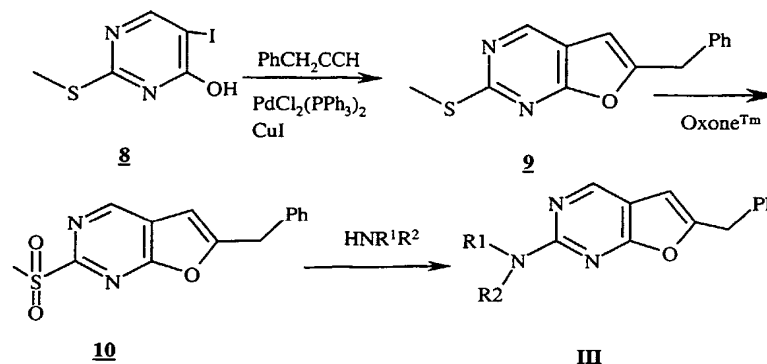
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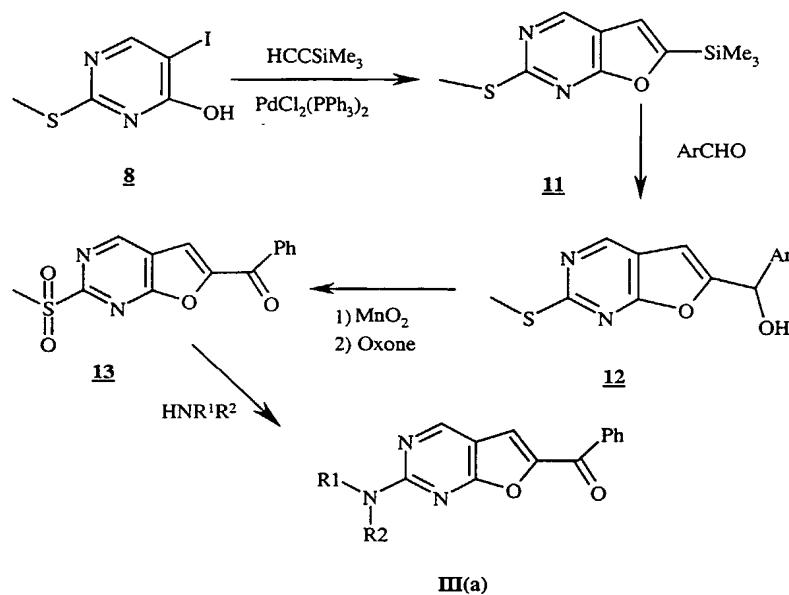
A furan analog of compound of formula I(a) can be prepared according to Scheme 3. A compound 8 (prepared according to methods described in Sakamoto, T.; Kondo, Y.; Watanabe, R.; Yamanaka, H.; *Chem. Pharm. Bull.* 1986, 34, 2719) can be converted to a compound 9 by palladium catalyzed coupling with alkynes and cyclization (see: Sakamoto, T.; Kondo, Y.; Watanabe, R.; Yamanaka, H.; *Chem. Pharm. Bull.* 1986, 34, 2719). Compound 9 is then oxidized to a compound 10 by methods described above. Compound 10 is then reacted with a desirable amine of formula HNR^1R^2 to afford a compound of formula III.

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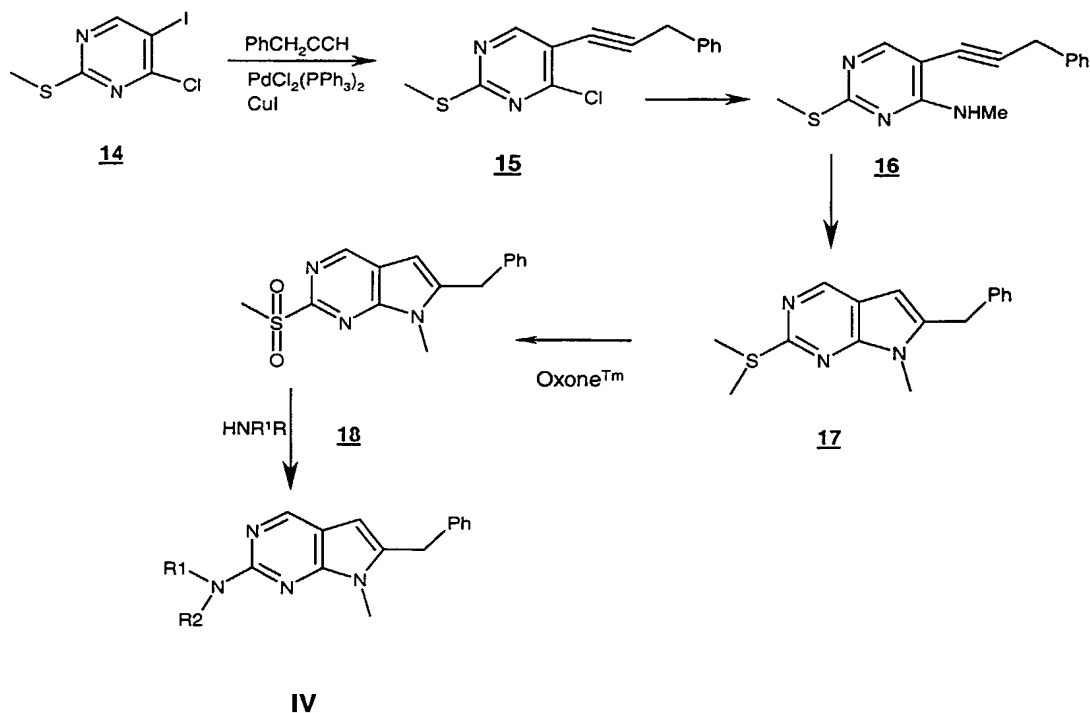
Scheme 3

Alternatively, compound 8 can be converted into a silyl furanopyrimidine of formula 11 which can be coupled with aryl aldehyde to give an alcohol of formula 12 by the procedure described in the literature. (Aquila, B.M.; *Tetrahedron Lett.* 1997, 38, 2795). Compound 12 is then converted into a sulfone 13 which can then be converted to a compound of formula III (a) by reaction with an amine of formula HNR^1R^2 . Compound III(a) is then converted into other derivatives thereof as described above in Scheme 1 and also by a number of routes available to those skilled in the art.

Scheme 3A

A compound of formula IV can be prepared according to Scheme 4. A compound of formula 14 (prepared according to methods described in Sakamoto, T.; Kondo, Y.; Watanabe, R.; Yamanaka, H.; *Chem. Pharm. Bull.* 1986, 34, 2719) is converted to a compound of formula 15 via a palladium catalyzed coupling reaction with an alkyne. Compound 15 is then treated with methylamine to afford compound 16. The cyclization of compound 16 to compound 17 can be accomplished by treatment with a mixture of CuI and PdCl₂(PPh₃)₂. Compound 17 is then converted to sulfone 18 and finally to a compound of formula IV by methods described in the previous schemes.

Scheme 4



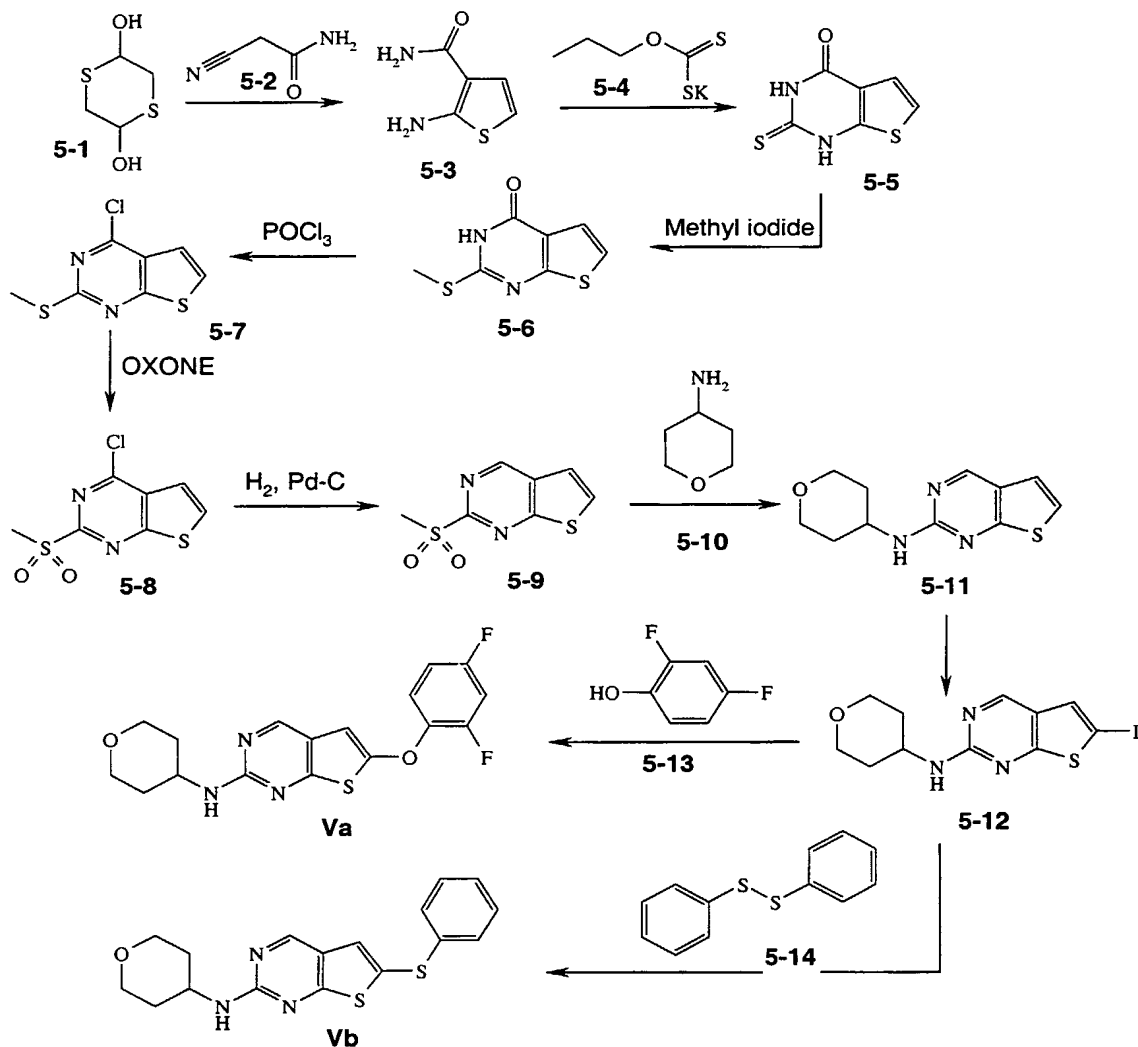
Compounds of formulas Va and Vb can be prepared according to Scheme 5.

A compound of formula 5-1 is reacted with α -cyanoacetamide of formula 5-2 to afford a thiophene compound of formula 5-3. The thiophene compound 5-3 is then reacted with a potassium salt of dithiocarbonic acid O-propyl ester of formula 5-4 to produce a thienopyrimidin-4-one of formula 5-5. Methylation of the

thienopyrimidin-4-one of formula 5-5 with methyl iodide then gave a corresponding thioether of formula 5-6. Oxidation and simultaneous chlorination of the thioether of formula 5-6 is then achieved using POCl_3 to afford thienopyrimidine of formula 5-7. Oxidation of the thioether of formula 5-7 to a sulfonyl compound of formula 5-8 is achieved using an oxidizing agent, e.g., Oxone. The chloro-substituent on the pyrimidine ring system is then reduced by hydrogenation using palladium on carbon catalyst to afford 2-methanesulfonyl-thieno[2,3-d]pyrimidine of formula 5-9. The methanesulfonyl group of formula 5-9 can be replaced with a desired amine compound to afford a desired amino-substituent. For example, as shown in Scheme 5, the methanesulfonyl group is displaced with 4-aminotetrahydropyran of formula 5-10 to yield 2-(tetrahydropyran-4-yl)amino-substituted thienopyrimidine of formula 5-11. This thienopyrimidine of formula 5-11 is then halogenated, e.g., using mercury (II) oxide and iodine, to afford iodo-substituted thienopyrimidine of formula 5-12. The iodo-substituted thienopyrimidine of formula 5-12 can be reacted with a variety of compounds, such as phenols (e.g., compound of formula 5-13, and its corresponding thiophenol compound, not shown) and for metalated by treatment with an organometallic reagent (e.g. alkyl lithiums) and subsequent reaction with disulfides (e.g., compound of formula 5-14), to yield a corresponding coupled products, e.g., compounds of formulas Va and Vb, respectively.

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Scheme 5



One of skill in the art will understand that certain modifications to the above schemes are contemplated and within the scope of the present invention. For example, certain steps will involve the use of protecting groups for functional groups that are not compatible with particular reaction conditions.

The compounds of formula I and the pharmaceutically acceptable salts of compounds of formula I can be used as medicaments, *e.g.* in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered enterally, *e.g.* orally in the form of tablets, coated tablets, dragées, hard and soft

gelatine capsules, solutions, emulsions or suspensions, nasally, *e.g.* in the form of nasal sprays, or rectally, *e.g.* in the form of suppositories. However, they may also be administered parenterally, *e.g.* in the form of injection solutions.

The compounds of formula I and their aforementioned pharmaceutically acceptable salts can be processed with pharmaceutically inert, organic or inorganic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like; depending on the nature of the active ingredient no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar, glucose and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

The pharmaceutical preparations can also contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain therapeutically valuable substances other than the compounds of formula I and their aforementioned pharmaceutically acceptable salts.

Medicaments which contain a compound of formula I or a pharmaceutically acceptable salt of a basic compound of formula I with an acid in association with a compatible pharmaceutical carrier material are also an object of the present invention, as is a process for the production of such medicaments which comprises bringing one or more of these compounds or salts and, if desired, one or more other therapeutically valuable substances into a galenical administration form together with a compatible pharmaceutical carrier.

As mentioned earlier, the compounds of formula I and their aforementioned pharmaceutically acceptable salts can be used in accordance with the invention as therapeutically active substances, especially as antiinflammatory agents or for the prevention of graft rejection following transplant surgery. The dosage can vary

within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of administration to adults a convenient daily dosage should be about 0.1 mg/kg to about 100 mg/kg, preferably about 0.5 mg/kg to about 5 mg/kg. The daily dosage may be administered as a single dose or in divided doses and, in addition, the upper dosage limit referred to earlier may be exceeded when this is found to be indicated.

Finally, the use of compounds of formula I and their aforementioned pharmaceutically acceptable salts for the production of medicaments, especially in the treatment or prophylaxis of inflammatory, immunological, oncological, bronchopulmonary, dermatological and cardiovascular disorders, in the treatment of asthma, central nervous system disorders or diabetic complications or for the prevention of graft rejection following transplant surgery, is also an object of the invention.

Compounds of Formula I are useful for, but not limited to, the treatment of any disorder or disease state in a human, or other mammal, which is exacerbated or caused by excessive or unregulated TNF or p38 kinase production by such mammal. Compounds of Formula I inhibit p38 kinase in in vitro assays and inhibit TNF- α release in cell based assays as described in Examples 12 and 13. Accordingly, the present invention provides a method of treating a cytokine-mediated disease which comprises administering an effective cytokine-interfering amount of a compound of Formula I, or a pharmaceutically acceptable salt or a tautomer thereof.

Compounds of Formula I are useful for, but not limited to, the treatment of inflammation in a subject, and for use as antipyretics for the treatment of fever.

Compounds of the invention are also useful in treating arthritis, including but not limited to, rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis, osteoarthritis, gouty arthritis and other arthritic conditions. In addition, compounds of the present invention are useful in treating pulmonary disorders or lung inflammation, including adult respiratory distress syndrome, pulmonary sarcoidosis, asthma, silicosis, and chronic pulmonary inflammatory disease. Furthermore, compounds of the present invention are also

useful in treating viral and bacterial infections, including sepsis, septic shock, gram negative sepsis, malaria, meningitis, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), pneumonia, and herpes virus. Moreover, compounds of the present invention are also useful in the treatment of bone resorption diseases, such as osteoporosis, endotoxic shock, toxic shock syndrome, reperfusion injury, autoimmune disease including graft vs. host reaction and allograft rejections, cardiovascular diseases including atherosclerosis, thrombosis, congestive heart failure, and cardiac reperfusion injury, renal reperfusion injury, liver disease and nephritis, and myalgias due to infection.

The compounds of the present invention are also useful for the treatment of influenza, multiple sclerosis, cancer, diabetes, systemic lupus erythematosus (SLE), skin-related conditions such as psoriasis, eczema, burns, dermatitis, keloid formation, and scar tissue formation. Compounds of the present invention are also useful in treating gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis. The compounds of the present invention can also be used in treating ophthalmic diseases, such as retinitis, retinopathies, uveitis, ocular photophobia, and of acute injury to the eye tissue. Compounds of the invention also would be useful for treatment of angiogenesis, including neoplasia; metastasis; ophthalmological conditions such as corneal graft rejection, ocular neovascularization, retinal neovascularization including neovascularization following injury or infection, diabetic retinopathy, retrolental fibroplasia and neovascular glaucoma; ulcerative diseases such as gastric ulcer; pathological, but non-malignant, conditions such as hemangiomas, including infantile hemangiomas, angiofibroma of the nasopharynx and avascular necrosis of bone; diabetic nephropathy and cardiomyopathy; and disorders of the female reproductive system such as endometriosis. In addition, compounds of the present invention are also useful for preventing the production of cyclooxygenase-2.

Besides being useful for human treatment, compounds of the present invention are also useful for veterinary treatment of companion animals, exotic

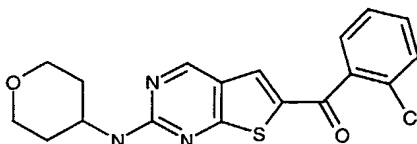
animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

Furthermore, compounds of the present invention can also be used in co-therapies, partially or completely, in place of other conventional antiinflammatories, such as together with steroids, cyclooxygenase-2 inhibitors, NSAIDs, DMARDS, immunosuppressive agents, 5-lipoxygenase inhibitors, LTB₄ antagonists and LTA₄ hydrolase inhibitors.

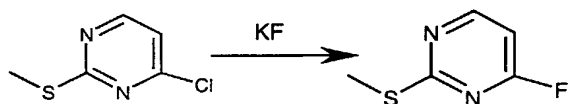
As used herein, the term "TNF mediated disorder" refers to any and all disorders and disease states in which TNF plays a role, either by control of TNF itself, or by TNF causing another monokine to be released, such as but not limited to IL-1, IL-6 or IL-8. A disease state in which, for instance, IL-1 is a major component, and whose production or action, is exacerbated or secreted in response to TNF, would therefore be considered a disorder mediated by TNF.

As used herein, the term "p38 mediated disorder" refers to any and all disorders and disease states in which p38 plays a role, either by control of p38 itself, or by p38 causing another factor to be released, such as but not limited to IL-1, IL-6 or IL-8. A disease state in which, for instance, IL-1 is a major component, and whose production or action, is exacerbated or secreted in response to p38, would therefore be considered a disorder mediated by p38.

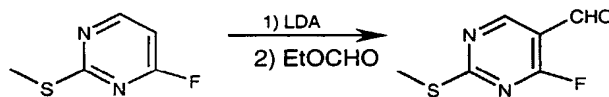
As TNF- β has close structural homology with TNF- α (also known as cachectin), and since each induces similar biologic responses and binds to the same cellular receptor, the synthesis of both TNF- α and TNF- β are inhibited by the compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically delineated otherwise.

EXAMPLESExample 12-(tetrahydropyran-4-ylamino)-6-(2-chlorobenzoyl)thieno[2,3-d]pyrimidine

This example illustrates the preparation of a compound of formula I by the method described under scheme 1.

Step 14-fluoro-2-methylthiopyrimidine

To a solution of 35.7 g (0.22 mol) of 4-chloro-2-methylthiopyrimidine (Aldrich Chemical Co., Milwaukee, Wisconsin, USA) in 135 mL of tetraglyme was added 18-crown-6 (1.33 g) and potassium fluoride (Anhydrous, Aldrich Chemical Co., Milwaukee, Wisconsin, USA, 80 g). The mixture was heated at 150°C with stirring for 16 hours. The mixture was then cooled and distilled under reduced pressure to give 20 g (62%) of 4-fluoro-2-methylthiopyrimidine as a liquid.

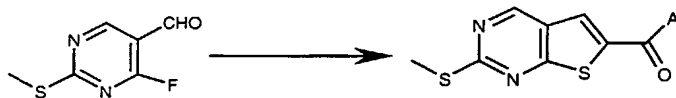
Step 24-fluoro-2-methylthiopyrimidine-5-carboxaldehyde

To THF (100 mL) at -78 °C was added 2.5 M n-butyl lithium (20.4 mL). The mixture was warmed to 0 °C and diisopropyl amine (8.2 mL) was added slowly. The mixture was stirred at 0 °C for 30 minutes and then cooled to -78 °C. A solution of 4-fluoro-2-methylthiopyrimidine (3.76 g, 22.2 mmol) in 5 mL of THF was slowly added and the mixture was stirred for 2 hours. Ethyl formate (4.3 mL,

44.4 mmol) was added and stirred for additional 2 hours. 4 N HCl (25 mL), ethanol (25 mL), and THF (100 mL) were slowly added and stirred for additional 10 min after the cooling bath was removed. The mixture was diluted with ethyl acetate (250 mL), water (200 mL), and saturated sodium bicarbonate (100 mL). The organic layer was separated and washed with brine (2x50 mL), dried over MgSO₄, and filtered. The solvent was removed to give a viscous oil (5.66 g).

Step3

2-(methylthio)-6-(aroyl)thieno[2,3-d]pyrimidine



To a 0 °C solution of the crude 4-fluoro-2-methylthiopyrimidine-5-carboxaldehyde obtained in step 2 (2.8 g, approximately 11 mmol) and triethyl amine (1.44 mL) in THF (40 mL) was slowly added a solution of 2'-chloro-2-thioacetophenone (1.93 g) in THF (30 mL), (prepared as described in Step 3A below). The mixture was then slowly warmed to room temperature and stirred overnight. The resulting solution was added to a mixture of ethylacetate (500 mL) and water (250 mL). The organic layer was separated, washed with brine and sodium bicarbonate solution, dried, and evaporated. The crude product was purified by column chromatography (silica gel, 5-10% EtOAc/hexane) to give the desired product (1.82 g), MP 137-140.4 °C; MS: 321 (M+H).

Step3A

2'-chloro-2-thioacetophenone

A mixture of 2'-chloroacetophenone (25 g, 0.162 mol) and copper bromide (72.8 g) in ethyl acetate (90 mL) and chloroform (90 mL) was refluxed for 2 hours. The mixture was cooled to room temperature, filtered through a pad of celite and washed with ethyl acetate. The solvents were removed to give crude 2-bromo-2'-chloroacetophenone (35 g).

A mixture of the above bromide (14.67 g) and potassium thioacetate (7.5 g) in acetone (250 mL) was stirred at room temperature overnight. Additional 3.7 g of

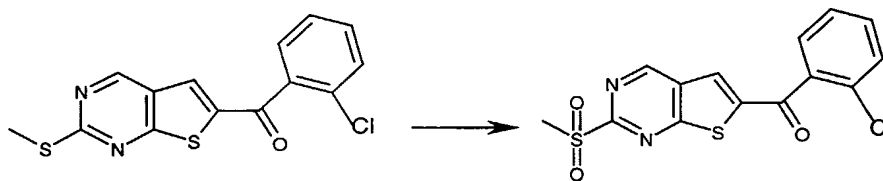
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potassium thioacetate was added and the mixture was stirred for another day. The reaction mixture was filtered and washed with acetone. The filtrate was evaporated, and the residue was diluted with ethyl acetate (200 mL) and brine (150 mL). The organic layer was separated, dried, and evaporated to give crude 2-(acetylthiol)-2'-chloroacetophenone (14.4 g).

To a solution of the above product (2.29 g, 10 mmol) in methanol (100 mL) was slowly added a solution of sodium thiomethoxide (0.7 g, 10 mmol) in methanol (10 mL). The reaction mixture was stirred for 2 hours and poured into 200 mL of 0.1 M HCl and extracted with dichloromethane (2x150 mL). The organic phase was washed with brine (150 mL), dried, and evaporated to give the crude 2'-chloro-2-thioacetophenone (1.93 g).

Step 4

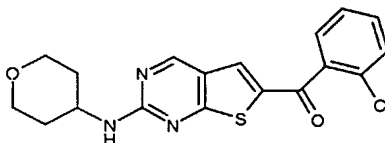
2-(methanesulfonyl)-6-(aroyl)thieno[2,3-d]Pyrimidine



To a solution of the sulfide (1.6 g) obtained in Step 3 in THF (80 mL) was added a solution of Oxone (Aldrich, 6.13 g) in water (40 mL) at 0 °C. The mixture was then stirred at room temperature for 5 hours. Ethyl acetate (250 mL) and water (150 mL) were added. The organic phase was separated, washed with water (2x150 mL), dried, and evaporated to give the sulfone (1.56 g), MP: 164.1-165.4 °C. MS: 352.9 (M+H).

Step 5

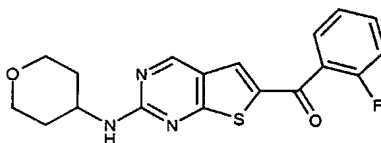
2-(tetrahydropyran-4-ylamino)-6-(2-chlorobenzoyl)thieno[2,3-d]pyrimidine



A mixture of the sulfone obtained above (352 mg) and 4-aminotetrahydropyran (152 mg) in NMP (0.1 mL) was heated at 100 °C for 3 hours. Ethyl acetate (180 mL) and water (50 mL) were added. The organic layer was separated, washed with brine, dried, and evaporated. The crude product was purified by preparative TLC (silica gel, 65% EtOAc/ hexanes) to give 253 mg of the final product. It was converted to the hydrochloride salt by treatment with 1.5 equivalents of 1N HCl in ether. MS: 374 (M+H).

Example 2

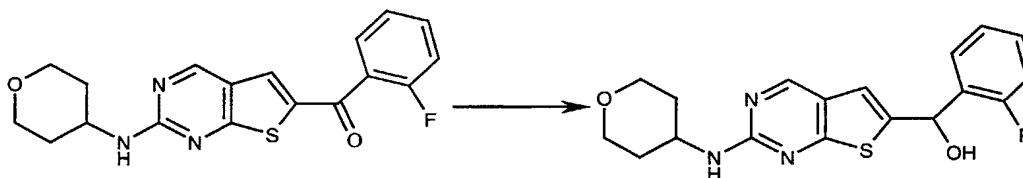
2-(tetrahydropyran-4-ylamino)-6-(2-fluorobenzoyl)thieno[2,3-d]pyrimidine



The above compound was prepared in a similar manner as described in example 1.

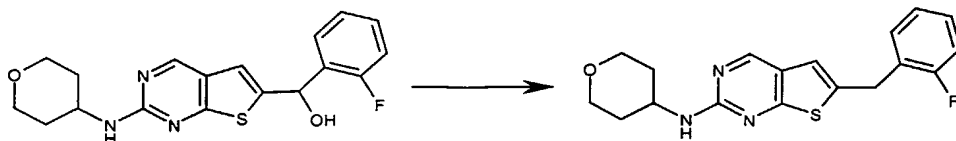
Example 2A

2-(tetrahydropyran-4-ylamino)-6-[(2-fluorophenyl)hydroxymethyl]thieno[2,3-d]pyrimidine

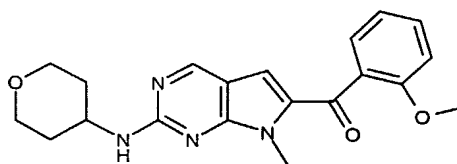


To a solution of 2-(tetrahydropyran-4-ylamino)-6-(2-fluorobenzoyl)thieno[2,3-d]pyrimidine (300 mg) in ethanol (30 mL) was added sodium borohydride (0.4 g) at room temperature and stirred overnight. Ethyl acetate (50 mL) was added to the reaction mixture. The organic layer was separated, washed with brine, dried, and evaporated. Purification by preparative TLC (silica gel, 50% EtOAc/hexanes) gave 140 mg of the alcohol. MS: 360.2 (M+H).

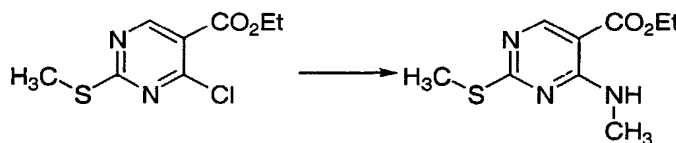
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Example 2B2-(tetrahydropyran-4-ylamino)-6-[(2-fluorophenyl)methyl]thieno[2,3-d]pyrimidine

The alcohol (140 mg) obtained in Example 2A was stirred with triethylsilane (1.0 mL) and trifluoroacetic acid (1.5 mL) in dichloromethane (5 mL) for 4 hours. The solvents were removed. The residue was diluted with toluene (5 mL) and then concentrated. This dilution-concentration process was repeated three times. Purification with preparative TLC (50% EtOAc/Hexanes) gave the final product. It was converted to the hydrochloride salt with 1N HCl in ether to yield 65 mg of the salt. MP: 217-219 °C. MS: 344 (M+H).

Example 32-(tetrahydropyran-4-ylamino)-6-(2-methoxybenzoyl)-7-methyl-pyrrolo[2,3-d]pyrimidine

This example illustrates the method of making a compound of formula I according to the method described in Scheme 2.

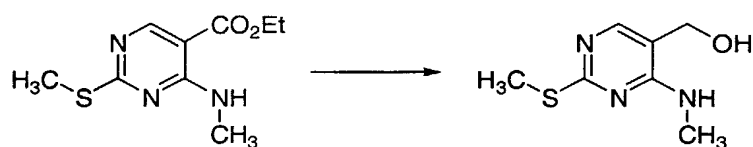
Step 1Ethyl 4-methylamino-2-methylthiopyrimidine-5-carboxylate

To a 0 °C solution of 20 g (86 mmol) of ethyl 4-chloro-2-methylthiopyrimidine-5-carboxylate (Aldrich Chemical Co., Milwaukee, Wisconsin, USA) in 250 mL of dichloromethane was slowly added 35 mL (281 mmol) of a 33%

solution of methylamine in ethanol. After stirring for 30 minutes, 150 mL of water was added and the phases were separated. The organic phase was dried over magnesium sulfate and filtered. The filtrate was evaporated under reduced pressure to give 19 g (97%) of ethyl 4-methylamino-2-methylthiopyrimidine-5-carboxylate as a white solid.

Step 2

4-methylamino-2-methylthiopyrimidine-5-methanol



To a suspension of lithium aluminum hydride (9 g, 237 mmol) in 300 mL of dry tetrahydrofuran was added dropwise a solution of 34 g (143 mmol) of ethyl 4-methylamino-2-methylthiopyrimidine-5-carboxylate in 300 mL of dry tetrahydrofuran and left to stand for 15 minutes. The mixture was cooled in an ice bath and 18 mL of water was added dropwise followed by 36 mL of 2 M sodium hydroxide solution and 48 mL of additional water. The resulting suspension was stirred for 17 hours at room temperature and then filtered. The filter residue was washed twice with 100 mL of ethyl acetate, and the combined filtrate and washings were evaporated under reduced pressure. The residue was suspended in 200 mL of dichloromethane/hexane (2:1) and the solid was filtered and dried to give 23.5 g (86%) of 4-methylamino-2-methylthiopyrimidine-5-methanol as a yellow solid.

Step 3

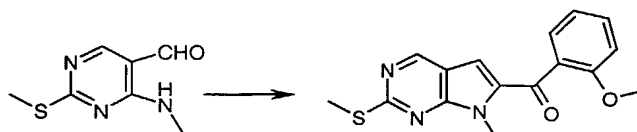
4-methylamino-2-methylthiopyrimidine-5-carboxaldehyde



To a solution of 4-methylamino-2-methylthiopyrimidine-5-methanol (20 g, 108 mmol) in 1 L of dichloromethane was added 87 g (1 mol) of manganese dioxide. The resulting suspension was stirred for 24 hours and then filtered through a filter

aid. The filter residue was washed with 100 mL of dichloromethane and the combined filtrate and washings were evaporated under reduced pressure to give 15.8 g (80%) of 4-methylamino-2-methylthiopyrimidine-5-carboxaldehyde as a white solid.

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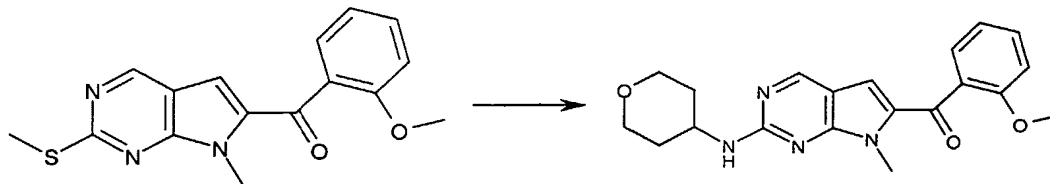
Step 42-(methylthio)-6-(2-methoxybenzoyl)-7-methyl-pyrrolo[2,3-d]pyrimidine

A mixture of the aldehyde (0.792 g), 2'-methoxy bromoacetophenone (1.17 g, Aldrich) and potassium carbonate (1.6 g) in NMP (5mL) was stirred at 70-80 °C overnight. Additional 2'-methoxy bromoacetophenone (0.88 g) was added and the mixture was stirred at 100 °C overnight. Additional 2'-methoxy bromoacetophenone (0.65 g) and potassium carbonate (1.12 g) were added and the mixture was again stirred at 100 °C overnight. The reaction mixture was cooled and diluted with ethyl acetate (150 mL) and washed with brine (3x50 mL), dried, and concentrated. Column chromatography (silica gel, 10-30% EtOAc/hexanes) followed by preparative TLC (silica gel, 30% EtOAc/hexanes) gave 100 mg of the product. MS: 334 (M+H).

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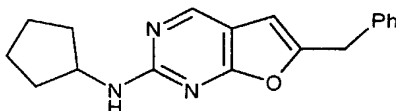
Step 52-(tetrahydropyran-4-ylamino)-6-(2-methoxybenzoyl)-7-methyl-pyrrolo[2,3-d]pyrimidine

The sulfide (0.1 g) obtained in the Step 4 above was stirred with oxone (0.5g) in THF/H₂O (2 mL/2 mL) for 4 hours. Aqueous workup with ethyl acetate and brine gave the crude sulfone.

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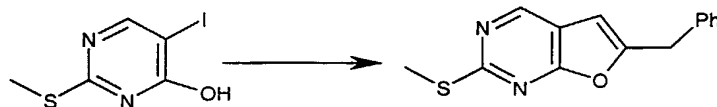
The sulfone obtained above was heated with 4-aminotetrahydropyran (0.18 g) in NMP (0.2 mL) at 140 °C overnight. An aqueous work up gave the crude product. Purification by preparative TLC gave the desired product (2 mg). MS: 367 (M+H).

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Example 42-(cyclopentylamino)-6-benzyl-furano[2,3-d]pyrimidine

This example illustrates the preparation of a compound of formula I according to that described under Scheme 3.

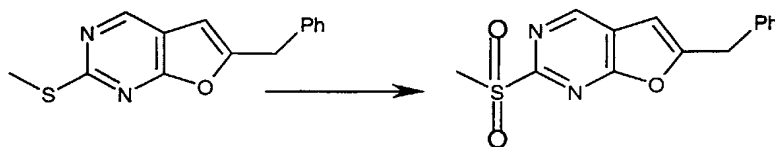
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Step 12-(methylthio)-6-benzyl-furano[2,3-d]pyrimidine

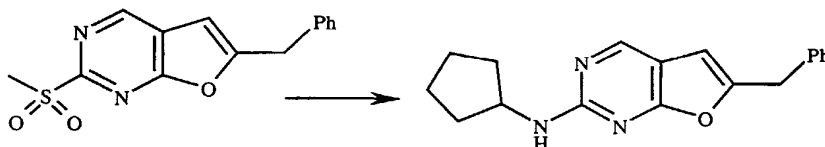
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A mixture of 2-methylthio-4-hydroxy-5-iodopyrimidine (2.65 g), 3-phenyl-1-propyne (1.49 mL), copper (I) iodide (90 mg) and bis(triphenylphosphine) Palladium (II) dichloride (Fluka, 160 mg) in 20 mL of triethylamine and NMP (7 mL) was stirred at 40 °C for 6 hours. The reaction mixture was diluted with ethyl acetate (100 mL), washed with brine (3x50 mL), concentrated and purified by column chromatography (5% EtOAc/hexanes) to give 0.57 g of a solid product. MP: 69-72.2 °C. MS: 257.2 (M+H).

20

Step 22-(cyclopentylamino)-6-benzyl-furano[2,3-d]pyrimidine

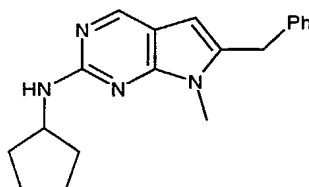
A solution of the sulfide (0.57 g) obtained in Step 1 above in THF (15 mL) was stirred with oxone (2.2 g) in water (15 mL) at 0 °C for 3 hours and at room temperature for 1 hour. An aqueous work up gave the crude sulfone (containing sulfoxide) (0.63 g).



A solution of the sulfone (60 mg) thus obtained in 1 mL of aminocyclopentane was stirred at 100 °C for 2 hours. The excess aminocyclopentane was removed. The crude product was purified by preparative TLC (40% EtOAc/hexanes) to give 47 mg of a solid product. MS: 294.2 (M+H).

Example 5

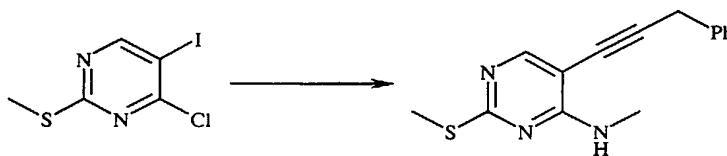
2-(cyclopentylamino)-6-benzyl-7-methyl-pyrrolo[2,3-d]pyrimidine



This example illustrates the preparation of 2-(cyclopentylamino)-6-benzyl-7-methyl-pyrrolo[2,3-d]pyrimidine according to that described in Scheme 4.

Step 1

2-methylthio-5-(3-phenylpropyn-1-yl)-6-methylaminopyrimidine



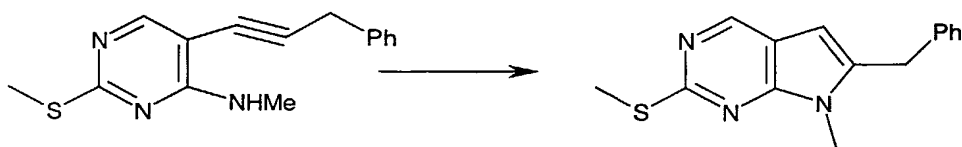
A mixture of 2-methanethio-4-chloro-5-iodopyrimidine (6.5 g), 3-phenyl-1-propyne (3.4 mL), copper (I) iodide (130 mg), bis(triphenylphosphine)palladium(II) dichloride (322 mg), and triethylamine (25 mL) was heated in NMP at 40 °C for 2 hours. The mixture was cooled to 0 °C and 25 mL of 40% methylamine (Aldrich) in

50

acetonitrile (15 mL) was added. The resulting mixture was stirred at room temperature for 2 hours and then concentrated. The residue was diluted with ethyl acetate (200 mL) and washed with brine (3x100 mL). The organic layer was separated, dried and evaporated to give an oil. Column chromatography purification (5-12% EtOAc/hexanes) gave 3.8 g of a solid product. MS: 270 (M+H).

Step 2

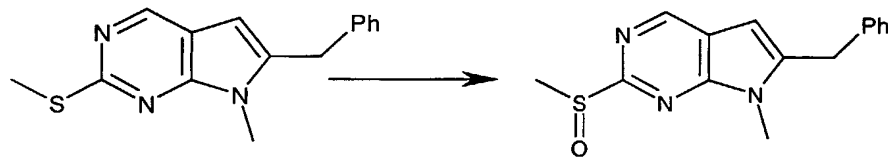
2-(methylthio)-6-benzyl-7-methyl-pyrrolo[2,3-d]pyrimidine



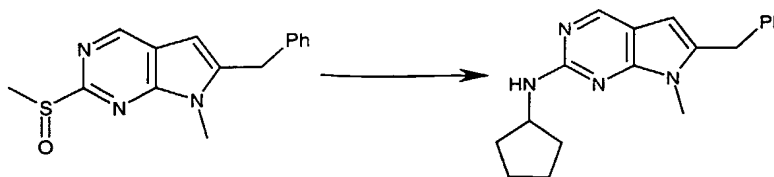
A mixture of the alkyne obtained above (3.47 g), triethylamine (15 mL), copper (I) iodide (200 mg), bis(triphenylphosphine)palladium dichloride (200 mg) in NMP (10 mL) was refluxed for 6 hours. Aqueous work up gave 4g of dark residue. Column chromatography purification (10-13% EtOAc/hexanes) gave 1.0 g of the product. MS: 270.2 (M+H).

Step 3

2-(methanesulfinyl)-6-benzyl-7-methyl-pyrrolo[2,3-d]pyrimidine

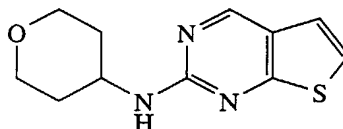
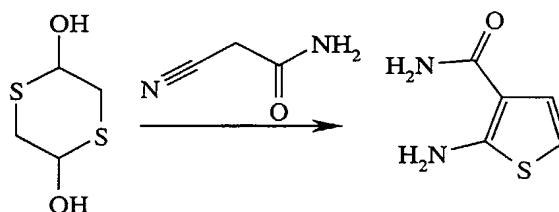


The sulfide (0.3 g) in THF (10 mL) was stirred with a solution of oxone (0.9 g) in water (10 mL) at 0-5 °C for 3 hours. Aqueous work up gave the sulfoxide (containing sulfone).

Step 42-(cyclopentylamino)-6-benzyl-7-methyl-pyrrolo[2,3-d]pyrimidine

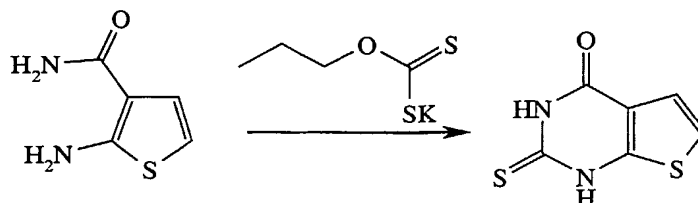
5 A mixture of the sulfoxide (50 mg) from Step 3 and cyclopentylamine (1 mL) was stirred at 100 °C overnight. Excess cyclopentylamine was removed and the residue was purified by preparative TLC (25% EtOAc/hexanes) to give the desired product (26 mg). MS: 307.3 (M+H).

Example 6

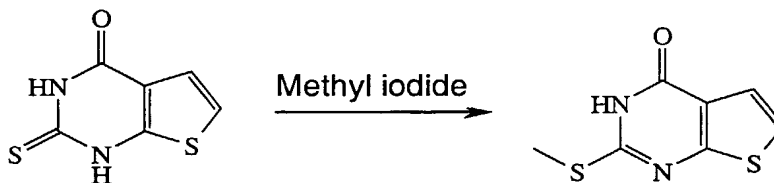
(Tetrahydropyran-4-yl)-thieno[2,3-d]pyrimidin-2-yl-amineStep12-Amino-thiophene-3-carboxylic acid amide

15 2,5-Dihydroxy-1,4-dithiane (76 g) and cyanoacetamide (84 g) were added to a mixture of methanol (180 mL), water (10 mL) and triethylamine (10 g). The resulting mixture was heated at 35-40 °C for about 30 minutes while stirring, and then heated to 50-60 °C for an additional 30 minutes with stirring. The reaction mixture was then cooled to room temperature and poured into a mixture of ice (100 g)/water (300 mL). A fine precipitate formed upon addition, which was filtered and dried overnight to give 100.6 g of the title compound as a pale gray powder ((M+H)⁺ = 143, M.P. = 159.0-159.6 °C).

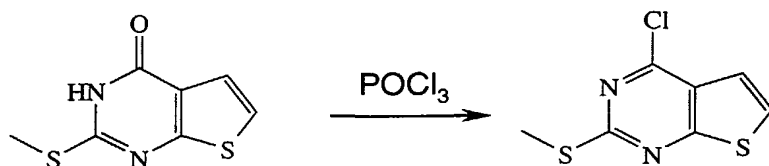
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Step22-Thioxo-2,3-dihydro-1H-thieno[2,3-d]pyrimidin-4-one

5 2-Amino-thiophene-3-carboxylic acid amide (28.4 g, 0.2 mol) and
 potassium ethylxanthate (96 g, 3 eq) were mixed together and added to DMF (1000
 mL). The resulting mixture was heated to 150 °C for about six hours. The solvent
 (DMF) was removed on the rotovap under high vacuum at 90 °C. The residue was
 diluted with 600 mL of aqueous citric acid (5%) and cooled to 0 °C and stirred for
 10 about 30 minutes. The tan powder was filtered and dried overnight to give 25.6g of
 the title compound ($(\text{M}+\text{H})^+ = 185$, M.P. >300 °C).

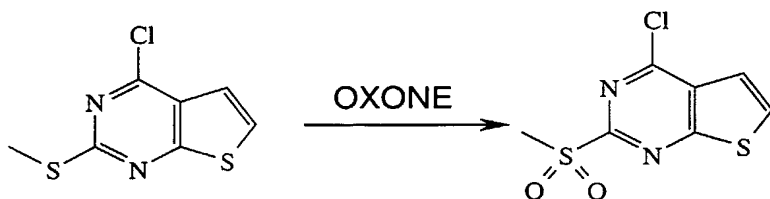
Step32-Methylsulfanyl-3H-thieno[2,3-d]pyrimidin-4-one

15 To a solution of 2-thioxo-2,3-dihydro-1H-thieno[2,3-d]pyrimidin-4-
 one (25.4 g, 0.138 mol) in 1N aqueous NaOH (600 mL) at room temperature was
 added methyl iodide (10.3 mL, 1.2 eq). The resulting mixture was stirred vigorously
 for about 2.5 hours. The reaction mixture was cooled to 0 °C and acetic acid was
 20 added (about 80 mL) until about pH=4.5 was reached. A fine precipitate was filtered
 and dried overnight to afford the title compound as a fine tan powder (24.8 g) ($\text{M}^+ =$
 198, M.P. = 231.6-235.0 °C).

Step44-Chloro-2-methylsulfanyl-thieno[2,3-d]pyrimidine

2-Methylsulfanyl-3H-thieno[2,3-d]pyrimidin-4-one (12 g, 60.5 mmol)

was combined with POCl₃ (56 mL), and the resulting mixture was heated to reflux for about 1 hour. The reaction mixture was concentrated under reduced pressure at 50 °C. The residue was diluted with ethyl acetate (700 mL) at 0 °C. Saturated sodium bicarbonate solution (600 mL) was added slowly. The resulting mixture was stirred vigorously at 0 °C for one hour and the layers were separated. Saturated sodium bicarbonate solution (600 mL) was added to the organic layer at 0 °C, and the mixture was stirred vigorously for 20 minutes. The layers were separated. Brine (600 mL) was added to the organic layer and stirred vigorously for 5 minutes, and the layers were again separated. The organic layer was dried over magnesium sulfate, filtered and concentrated to afford the title compound (10.7 g) as a dark tan powder ($M^+ = 216$, M.P. = 105.0-107.4 °C).

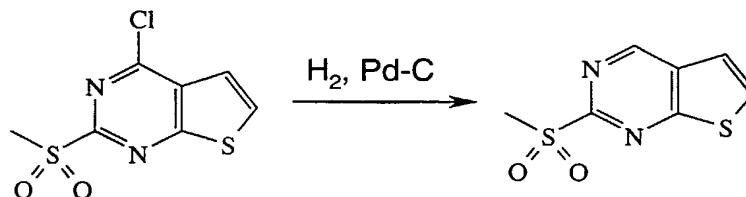
Step54-Chloro-2-methanesulfonyl-thieno[2,3-d]pyrimidine

To a solution of 4-chloro-2-methylsulfanyl-thieno[2,3-d]pyrimidine (10 g, 46.15 mmol) in tetrahydrofuran (350 mL) at 0 °C was added a solution of OXONE (59.6 g, 2.1 eq) in water (300 mL) dropwise with stirring. The resulting mixture was gradually warmed from 0 °C to room temperature overnight. The reaction mixture was diluted with ethyl acetate (1000 mL) and water (300 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate

(1x300 mL). Organic layers were combined, washed with brine (2x300 mL), dried over magnesium sulfate, filtered and concentrated to give 10.7g of the title compound as a tan powder $(M+H)^+=249$.

5 Step6

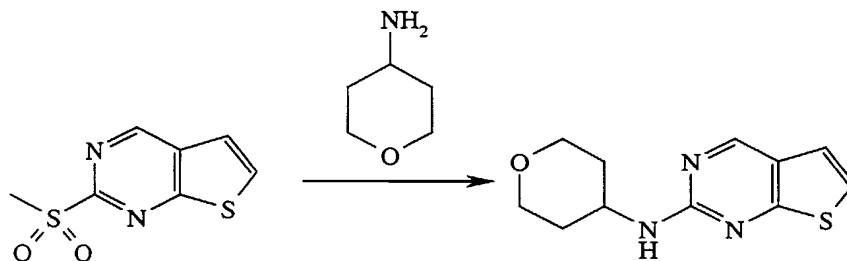
2-Methanesulfonyl-thieno[2,3-d]pyrimidine



Nitrogen gas was bubbled through a solution of 4-chloro-2-methanesulfonyl-thieno[2,3-d]pyrimidine (2.8 g) in ethanol (400 mL) and tetrahydrofuran (75 mL) for 5 minutes. To this solution was added 10% palladium on activated charcoal (2.8 g). The resulting mixture was placed on a Parr shaker under 30 psi of hydrogen gas. After 16 hours, additional catalyst (1 g) was added, and the mixture was again placed on the Parr shaker under 30 psi hydrogen gas for additional 6 hours. The reaction mixture was filtered through a 3 cm bed of celite. The filter cake was washed with dichloromethane. Concentration of the filtrate gave the title compound (2.2 g).

20 Step7

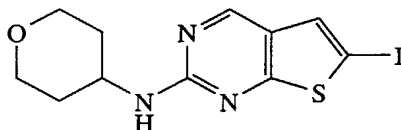
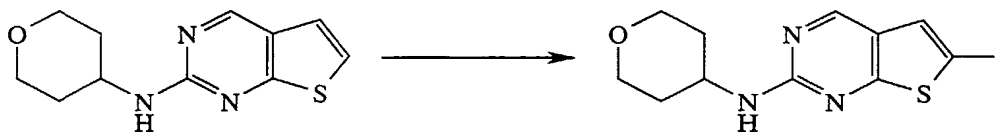
(Tetrahydropyran-4-yl)-thieno[2,3-d]pyrimidin-2-yl-amine



A mixture of 2-methanesulfonyl-thieno[2,3-d]pyrimidine (1.58 g, 7.37 mmol), 4-aminotetrahydropyran (2.24 g, 3 eq) and 1-methyl-2-pyrrolidinone (2 mL) was heated to 100 °C with stirring for about 7 hours and continued heating at 80 °C

overnight. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (180 mL)/water (60 mL). The layers were separated, and the organic layer was washed successively with water (4x60 mL) and brine (1x60 mL). The organic layer was then dried over magnesium sulfate, filtered and concentrated to give 1.7 g of the crude product. Purification by column chromatography on silica gel eluting with 25% ethyl acetate in hexanes afforded the title compound as a white powder (1.264 g) ($(M+H)^+ = 236$, M.P. = 127.0-130.0 °C).

Example 7

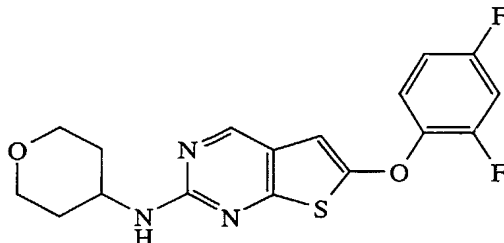
6-Iodo-thieno[2,3-d]pyrimidin-2-yl)-(tetrahydropyran-4-yl)-amineStep16-Iodo-thieno[2,3-d]pyrimidin-2-yl)-(tetrahydropyran-4-yl)-amine

To a solution of (tetrahydro-pyran-4-yl)-thieno[2,3-d]pyrimidin-2-yl-amine (786 mg, 3.34 mmol) in benzene (40 mL) was added mercury(II) oxide (854 mg, 1.18 eq) followed by iodine (1.00 g, 1.18 eq). The resulting mixture was stirred vigorously at room temperature overnight. Additional mercury(II) oxide (427 mg, 0.6 eq) and iodine (500 mg, 0.6 eq) were added, and the mixture was again stirred vigorously at room temperature for one additional day. The reaction mixture was then filtered through a 3 cm bed of celite and washed with ethyl acetate (180 mL). The filtrate was washed successively with saturated aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$ (4x50 mL), water (2x50 mL) and brine (1x50 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated to give the title compound as a reddish powder (823 mg) ($(M+H)^+ = 362$).

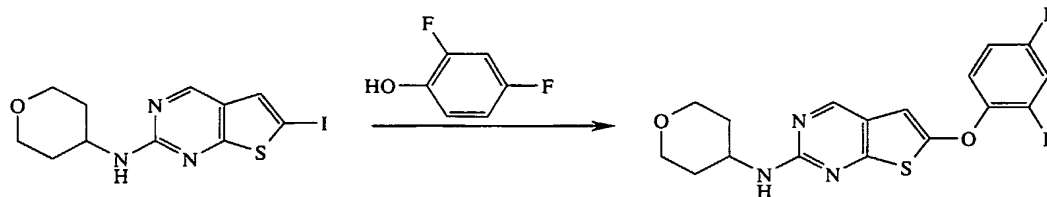
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Example 8

[6-(2,4-Difluorophenoxy)thieno[2,3-d]pyrimidin-2-yl]-(tetrahydropyran-4-yl)-amine

5 Step1

[6-(2,4-Difluorophenoxy)thieno[2,3-d]pyrimidin-2-yl]-(tetrahydropyran-4-yl)-amine

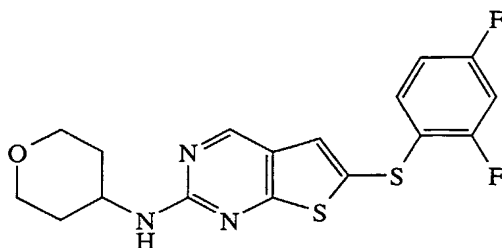


A mixture of 2,4-difluorophenol (0.5 mL, 38 eq), sodium hydride (205 mg, 37 eq) and 1-methyl-2-pyrrolidinone (0.6 mL) in a 2.5 mL microwave reactor vessel was stirred for about 5 minutes. To this mixture was added 6-iodo-thieno[2,3-d]pyrimidin-2-yl]-(tetrahydropyran-4-yl)-amine (50 mg, 0.14 mmol), and the resulting mixture was placed on a microwave reactor for 75 minutes at 150 °C. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate (85 mL) and washed successively with water (3x30 mL) and brine (1x30 mL). The ethyl acetate layer was concentrated and then purified by Preparative Thin Layer Chromatography eluting on two (20x20 cm, 1000 μ M) silica gel plates with 40% ethyl acetate in hexanes. The title compound was isolated as an off-white powder (8 mg) $(M+H)^+ = 364$.

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Example 9

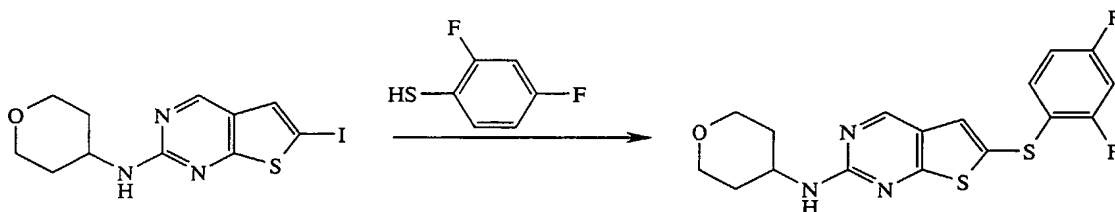
[6-(2,4-Difluorophenylsulfanyl)thieno[2,3-d]pyrimidin-2-yl]-(tetrahydropyran-4-yl)-amine



5

Step1

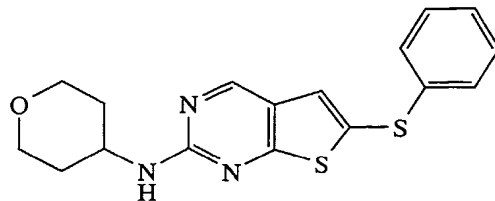
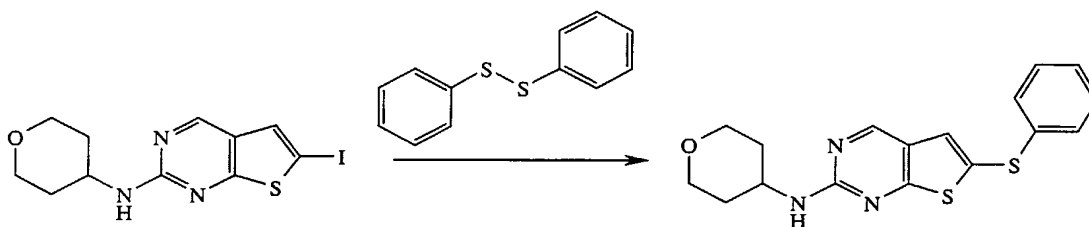
[6-(2,4-Difluorophenylsulfanyl)thieno[2,3-d]pyrimidin-2-yl]-(tetrahydropyran-4-yl)-amine



2,4-Difluorobenzenethiol (0.35 mL, 10.8 eq) was added to 6-iodo-thieno[2,3-d]pyrimidin-2-yl)-(tetrahydropyran-4-yl)-amine (100 mg, 0.277 mmol), and the resulting mixture was stirred overnight at room temperature. The reaction mixture was then heated 100 °C with stirring for 5 hours, after which 1-methyl-2-pyrrolidinone (0.2 mL) was added followed by potassium carbonate (415 mg, 10.8 eq). The resulting mixture was heated with stirring to 150 °C for an additional 5 hours. The reaction mixture was then cooled to room temperature and diluted with ethyl acetate (35 mL)/water (20 mL). The layers were separated. The organic layer was washed with successively with water (3x20 mL) and brine (1x20 mL), dried over magnesium sulfate, filtered and concentrated to yield a crude product (452 mg), which was purified by Preparative Thin Layer Chromatography eluting on four (20x40 cm, 1000 μ M) silica gel plates with 55% ethyl acetate in hexanes to afford the title compound (16 mg) as an off-white powder $(M+H)^+ = 380$.

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Example 10

(6-Phenylsulfanyltieno[2,3-d]pyrimidin-2-yl)-(tetrahydropyran-4-yl)-amine5 Step1(6-Phenylsulfanyltieno[2,3-d]pyrimidin-2-yl)-(tetrahydropyran-4-yl)-amine

To a solution of 6-iodothieno[2,3-d]pyrimidin-2-yl)-(tetrahydropyran-4-yl)-amine (100 mg, 0.277 mmol) in tetrahydrofuran (3 mL) at -78 °C was added 2.5M n-butyllithium in hexanes (0.23 mL, 2.1 eq) dropwise. The reaction mixture turned from red to yellow. The resulting mixture was stirred at -78 °C for 45 minutes before slowly adding a solution of phenyl disulfide (242 mg, 4 eq) in tetrahydrofuran (3 mL) at -78 °C. The reaction was gradually warmed from -78 °C to room temperature over 4 hours and quenched by adding water (5 mL). The resulting mixture was diluted with ethyl acetate (35 mL)/water (25 mL). The layers were partitioned, and the separated organic layer was washed with brine (1x20 mL), dried over magnesium sulfate, filtered and concentrated to give the crude product. Purification by Preparative Thin Layer Chromatography eluting on two (20x20 cm, 1000 μ M) silica gel plates with 50% ethyl acetate in hexanes afforded the title compound (16 mg) as an off-white powder $(M+H)^+ = 344$.

Example 11

The following are representative pharmaceutical formulations containing a compound of Formula (I).

Tablet formulation

The following ingredients are mixed intimately and pressed into single scored tablets.

5		Quantity per
	Ingredient	tablet, mg
	compound of this invention	400
	cornstarch	50
	croscarmellose sodium	25
10	lactose	120
	magnesium stearate	5

Capsule formulation

The following ingredients are mixed intimately and loaded into a hard-shell gelatin capsule.

15		Quantity per
	Ingredient	capsule, mg
	compound of this invention	200
20	lactose, spray-dried	148
	magnesium stearate	2

Suspension formulation

The following ingredients are mixed to form a suspension for oral administration.

	Ingredient	Amount
5	compound of this invention	1.0 g
	fumaric acid	0.5 g
	sodium chloride	2.0 g
	methyl paraben	0.15 g
	propyl paraben	0.05 g
10	granulated sugar	25.5 g
	Sorbitol (70% solution)	12.85 g
	Veegum K (Vanderbilt Co.)	1.0 g
	flavoring	0.035 ml
	colorings	0.5 mg
15	distilled water	q.s. to 100 ml

Injectable formulation

The following ingredients are mixed to form an injectable formulation.

	Ingredient	Amount
20	compound of this invention	0.2 g
	sodium acetate buffer solution, 0.4 M	2.0 ml
	HCl (1N) or NaOH (1N)	q.s. to suitable pH
	water (distilled, sterile)	q.s. to 20 ml

25

All of the above ingredients, except water, are combined and heated to 60-70 °C with stirring. A sufficient quantity of water at 60 °C is then added with vigorous stirring to emulsify the ingredients, and water then added q.s. to 100 g.

Suppository formulation

A suppository of total weight 2.5 g is prepared by mixing the compound of the invention with Witepsol® H-15 (triglycerides of saturated vegetable fatty acid; Riches-Nelson, Inc., New York), and has the following composition:

5

compound of the invention	500 mg
Witepsol® H-15	balance

Example 12

10

Inhibition Of p-38 (MAP) Kinase-In Vitro Assay

The p-38 MAP kinase inhibitory activity of compounds of this invention *in vitro* was determined by measuring the transfer of the γ -phosphate from γ -³³P-ATP by p-38 kinase to Myelin Basic Protein (MBP), using the a minor modification of the method described in Ahn, N. G.; et al. *J. of Biol. Chem.* Vol. 266(7), 4220-4227, (1991)

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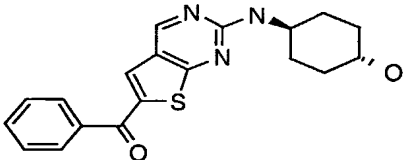
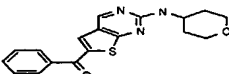
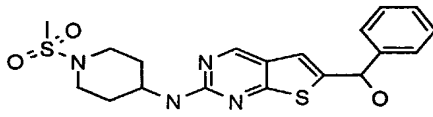
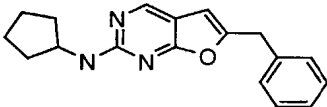
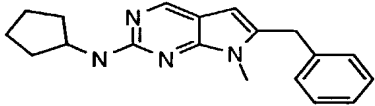
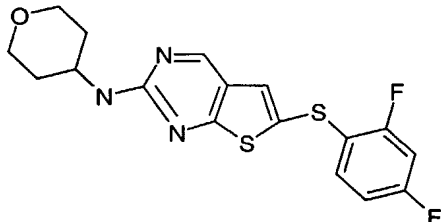
The phosphorylated form of the recombinant p38 MAP kinase was expressed with SEK-1 and MEKK in E. Coli (*see*, Khokhlatchev, A. et al. *J. of Biol. Chem.* Vol. 272(17), 11057-11062, (1997) and then purified by affinity chromatography using a Nickel column.

20

The phosphorylated p38 MAP kinase was diluted in kinase buffer (20 mM 3-(N-morpholino)propanesulfonic acid, pH 7.2, 25 mM β -glycerol phosphate, 5 mM ethylene glycol-bis(beta-aminoethyl ether)-N,N,N',N'-tetraacetic acid, 1mM sodium vanadate, 1mM dithiothreitol, 40mM magnesium chloride). Test compound dissolved in DMSO or only DMSO (control) was added and the samples were incubated for 10 min. at 30 °C. The kinase reaction was initiated by the addition of a substrate cocktail containing MBP and γ -³³P-ATP. After incubating for an additional 25 20 min. at 30 °C, the reaction was terminated by adding 0.75% phosphoric acid. The phosphorylated MBP was then separated from the residual γ -³³P-ATP using a phosphocellulose membrane (Millipore, Bedford, MA) and quantitated using a scintillation counter (Packard, Meriden, CT).

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The p-38 inhibitory activities (expressed as IC₅₀, the concentration causing 50% inhibition of the p-38 enzyme being analyzed) of the compounds listed in Table 1 in the specification are between 0.01 μ M and 10 μ M.

Compound	Structure	p38 IC ₅₀ (nM)
1		104
3		221
23		128
30		744
33		135
41		226

Example 13

This example illustrates an *in vitro* assay to evaluate the inhibition of LPS-induced TNF- α production in THP1 cells.

The ability of the compounds of this invention to inhibit the TNF- α release was determined using a minor modification of the methods described in Blifeld, *et al. Transplantation*, 51:498-503 (1991).

(a) Induction of TNF biosynthesis:

THP-1 cells were suspended in culture medium [RPMI (Gibco-BRL, Gaithersburg, MD, USA) containing 15% fetal bovine serum, 0.02 mM 2-mercaptoethanol], at a concentration of 2.5×10^6 cells/mL and then plated in 96 well plate (0.2 mL aliquots in each well). Test compounds were dissolved in DMSO and then diluted with the culture medium such that the final DMSO concentration was 5%. Twenty five μ L aliquots of test solution or only medium with DMSO (control) were added to each well. The cells were incubated for 30 min., at 37 °C. LPS (Sigma, St. Louis, MO, USA) was added to the wells at a final concentration of 0.5 μ g/mL, and cells were incubated for an additional 2 h. At the end of the incubation period, culture supernatants were collected and the amount of TNF- α present was determined using an ELISA assay as described below.

(b) ELISA Assay:

The amount of human TNF- α present was determined by a specific trapping ELISA assay using two anti-TNF- α antibodies (2TNF-H12 and 2TNF-H34) described in Reimund, J. M., et al. *GUT*. Vol. 39(5), 684-689 (1996).

Polystyrene 96-well plates were coated with 50 μ L per well of antibody 2TNF-H12 in PBS (10 μ g/mL) and incubated in a humidified chamber at 4 °C overnight. The plates were washed with PBS and then blocked with 5% nonfat-dry milk in PBS for 1 hour at room temperature and washed with 0.1% BSA (bovine serum albumin) in PBS.

TNF standards were prepared from a stock solution of human recombinant TNF- α (R&D Systems, Minneapolis, MN, USA). The concentration of the standards in the assay began at 10 ng/mL followed by 6 half log serial dilutions.

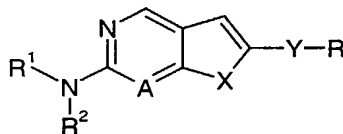
Twenty five μL aliquots of the above culture supernatants or TNF standards or only medium (control) were mixed with 25 μL aliquots of biotinylated monoclonal antibody 2TNF-H34 (2 $\mu\text{g}/\text{mL}$ in PBS containing 0.1% BSA) and then added to each well. The samples were incubated for 2 hr at room temperature with gentle shaking and then washed 3 times with 0.1% BSA in PBS. 50 μL of peroxidase-streptavidin (Zymed, S. San Francisco, CA, USA) solution containing 0.416 $\mu\text{g}/\text{mL}$ of peroxidase-streptavidin and 0.1% BSA in PBS was added to each well. The samples were incubated for an additional 1 hr at room temperature and then washed 4 times with 0.1% BSA in PBS. Fifty μL of O-phenylenediamine solution (1 $\mu\text{g}/\text{mL}$ O-phenylene-diamine and 0.03 % hydrogen peroxide in 0.2M citrate buffer pH 4.5) was added to each well and the samples were incubated in the dark for 30 min., at room temperature. Optical density of the sample and the reference were read at 450 nm and 650 nm, respectively. TNF- α levels were determined from a graph relating the optical density at 450 nm to the concentration used.

The IC_{50} value was defined as the concentration of the test compound corresponding to half-maximal reduction in 450 nm absorbance.

65

Claims

1. A compound represented by formula I:



5 wherein:

A is N or CH;

R¹ is hydrogen, alkyl or arylalkyl;

R² is alkyl, hydroxyalkyl, (R'')₂NCO-alkylene- (where each R'' is independently hydrogen or alkyl), cycloalkyl, heterocyclyl, aryl, heteroaryl or heteroalkyl;

X is O, NR³ or S, wherein R³ is hydrogen, alkyl or aryl; and

Y is a bond, O, NR', C(=O), CH(OR'), CH(R'), or S(O)_n, wherein n is 0, 1, or 2; and R' is hydrogen or alkyl; and

R is aryl or heteroaryl; or

an isomer, a pharmaceutically acceptable salt, an ester or a prodrug thereof.

2. The compound according to claim 1 wherein all substituents have the same meaning as defined in claim 1 except for R² not being heteroalkyl.

3. The compound according to claim 1 wherein:

A is N or CH;

R¹ is hydrogen, alkyl or arylalkyl;

R² is alkyl, hydroxyalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl;

X is O, NR³ or S, wherein R³ is hydrogen or methyl; and

Y is O, NR', C(=O), CH(OR'), CH(R'), or S(O)_n, wherein n is 0, 1, or 2; and R' is hydrogen or alkyl; and

R is aryl or heteroaryl.

4. The compound according to any one of claims 1 to 3 wherein:

A is N;

R¹ is hydrogen;

R² is hydroxyalkyl, cycloalkyl, heterocyclyl, aryl or heteroalkyl;

X is O, NR³ or S, wherein R³ is alkyl or aryl; and

5 Y is a bond, O, C(=O), CH(OR'), CH(R'), or S and R' is hydrogen; and
R is aryl.

5. The compound according to any one of claims 1 to 4, wherein:

Y is CH₂ or C(=O); and R is optionally substituted phenyl.

10

6. The compound according to any one of claims 1 to 5, wherein A is N.

7. The compound according any one of claims 1 to 6, wherein X is S.

15

8. The compound according to any one of claims 1 to 7, wherein R is phenyl which is optionally substituted with alkyl, hydroxyalkyl, halo, trifluoromethyl, alkoxy, trifluoromethoxy, cyano, nitro or amino.

20 9. The compound according to any one of claims 1 to 8, wherein Y is C(=O).

10. The compound according to any one of claims 1 to 9, wherein R¹ is a hydrogen.

25 11. The compound according to any one of claims 1 to 10, wherein R² is selected from the group consisting of cycloalkyl, heterocyclyl, aryl and heteroaryl.

12. The compound according to any one of claims 1 to 11, wherein R² is heterocyclyl.

30

13. The compound according to any one of claims 1 to 4, wherein Y is O or S.

14. The compound according to Claim 13, wherein A is N.

15. The compound according to Claim 13 or 14, wherein X is S.

16. The compound according to any one of claims 13 to 15, wherein R² is heterocyclyl.

17. The compound according to any one of claims 13 to 16, wherein R is aryl.

18. The compound according to any one of claims 13 to 17, wherein R is optionally substituted phenyl.

19. The compound according to any one of claims 13 to 18, wherein R¹ is hydrogen.

20. The compound according to any one of claims 1, 2 or 4, where in Y is a bond.

21. The compound according to Claim 20, wherein X is O or NR³.

22. The compound according to Claim 20 or 21, wherein R² is heterocyclyl or aryl.

23. The compound according to any one of claims 20 to 23, wherein R³ is phenyl.

24. The compound according to Claims 1 to 4, wherein R is aryl.

25. The compound according to Claim 24, wherein R is optionally substituted phenyl.

5 26. The compound according to Claim 24 or 25, wherein A is N.

27. The compound according to any one of claims 24 to 26, wherein R¹ is hydrogen.

10 28. The compound according to any one of claims 24 to 27, wherein R² is alkyl, hydroxyalkyl, cycloalkyl, heterocyclyl or aryl.

29. The compound according to any one of claims 24 to 27, wherein R³ is methyl or phenyl.

15 30. The compound according to any one of claims 1 to 4, wherein A is N.

31. The compound according to Claim 30, wherein R is aryl.

20 32. The compound according to Claim 30 or 31, wherein R² is alkyl, hydroxyalkyl, cycloalkyl, heterocyclyl or aryl.

33. The compound according to any one of claims 30 to 32, wherein R¹ is hydrogen.

25 34. The compound according to any one of claims 1 to 3, wherein R is thiophene.

30 35. The compound according to any one of claims 1 to 3, wherein:
R¹ is hydrogen, R² is 4-hydroxycylcohexyl, A is N, X is S, Y is C(=O), and R is phenyl;

R^1 is hydrogen, R^2 is 4-(N-methylsulfonylpiperidinyl), A is N, X is S, Y is C(=O), and R is phenyl;

R^1 is hydrogen, R^2 is 4-tetrahydropyranyl, A is N, X is S, Y is C(=O), and R is phenyl;

5 R^1 is hydrogen, R^2 is 4-tetrahydropyranyl, A is N, X is S, Y is C(=O), and R is 4-fluorophenyl;

R^1 is hydrogen, R^2 is 4-tetrahydropyranyl, A is N, X is S, Y is C(=O), and R is 2-chlorophenyl;

10 R^1 is hydrogen, R^2 is 4-(N-methylsulfonylpiperidinyl), A is N, X is S, Y is C(=O), and R is 2-fluorophenyl;

R^1 is hydrogen, R^2 is 4-(N-methylsulfonylpiperidinyl), A is N, X is S, Y is C(=O), and R is 3-fluorophenyl;

R^1 is hydrogen, R^2 is 4-tetrahydropyranyl, A is N, X is S, Y is C(=O), and R is 3-fluorophenyl;

15 R^1 is hydrogen, R^2 is 4-tetrahydropyranyl, A is N, X is S, Y is C(=O), and R is 2-fluorophenyl;

R^1 is hydrogen, R^2 is 1-(1,1-dimethyl-2-hydroxy)ethyl, A is N, X is S, Y is C(=O), and R is 2-fluorophenyl;

20 R^1 is hydrogen, R^2 is 4-tetrahydropyranyl, A is N, X is S, Y is C(=O), and R is 4-chlorophenyl;

R^1 is hydrogen, R^2 is 4-(N-methylsulfonylpiperidinyl), A is N, X is S, Y is C(=O), and R is 4-fluorophenyl;

R^1 is hydrogen, R^2 is 4-(N-methylsulfonylpiperidinyl), A is N, X is S, Y is C(=O), and R is 4-chlorophenyl;

25 R^1 is hydrogen, R^2 is 4-(N-methylsulfonylpiperidinyl), A is N, X is S, Y is C(=O), and R is 2-chlorophenyl;

R^1 is hydrogen, R^2 is 4-tetrahydro-1,1-dioxide-2-H-thiopyranyl, A is N, X is S, Y is C(=O), and R is 2-fluorophenyl;

30 R^1 is hydrogen, R^2 is 4-tetrahydro-1,1-dioxide-2-H-thiopyranyl, A is N, X is S, Y is C(=O), and R is 3-fluorophenyl;

R^1 is hydrogen, R^2 is 1-(1,1-dimethyl-2-hydroxy)ethyl, A is N, X is S, Y is C(=O), and R is 3-fluorophenyl;

R^1 is hydrogen, R^2 is 1-(1-methyl-2-methoxy)ethyl, A is N, X is S, Y is C(=O), and R is 3-fluorophenyl;

5 R^1 is hydrogen, R^2 is 1-(1-methyl-2-hydroxy)ethyl, A is N, X is S, Y is C(=O), and R is 3-fluorophenyl;

R^1 is hydrogen, R^2 is 1-(1-methyl-2,2-dimethyl-2-hydroxy)ethyl, A is N, X is S, Y is C(=O), and R is 2-chlorophenyl;

10 R^1 is hydrogen, R^2 is 1-(1-methyl-2,2-dimethyl-2-hydroxy)ethyl, A is N, X is S, Y is C(=O), and R is 2-fluorophenyl;

R^1 is hydrogen, R^2 is 4-(N-methylsulfonylpiperidinyl), R' is hydrogen, A is N, X is S, Y is CHR' , and R is phenyl;

R^1 is hydrogen, R^2 is 4-(N-methylsulfonylpiperidinyl), R' is hydrogen, A is N, X is S, Y is $CH(OR')$, and R is phenyl;

15 R^1 is hydrogen, R^2 is 4-tetrahydropyranyl, R' is hydrogen, A is N, X is S, Y is $CH(OR')$, and R is 2-fluorophenyl;

R^1 is hydrogen, R^2 is 4-tetrahydropyranyl, R' is hydrogen, A is N, X is S, Y is CHR' , and R is 2-fluorophenyl;

20 R^1 is hydrogen, R^2 is 4-tetrahydropyranyl, A is N, X is S, Y is C(=O), and R is 2-methylphenyl;

R^1 is hydrogen, R^2 is 4-tetrahydropyranyl, A is N, X is S, Y is C(=O), and R is 2-methoxyphenyl;

R^1 is hydrogen, R^2 is 4-tetrahydropyranyl, A is N, X is S, Y is C(=O), and R is 3-methoxyphenyl;

25 R^1 is hydrogen, R^2 is 4-tetrahydropyranyl, R' is hydrogen, A is N, X is O, Y is CHR' , and R is phenyl;

R^1 is hydrogen, R^2 is cyclopentyl, R' is hydrogen, A is N, X is O, Y is CHR' , and

R is phenyl;

30 R^1 is hydrogen, R^2 is 4-hydroxycyclohexyl, R' is hydrogen, A is NR^3 , X is O, Y is CHR' , and R is phenyl;

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R^1 is hydrogen, R^2 isopropyl, R' is hydrogen, A is N, X is O, Y is CHR' , and R is phenyl;

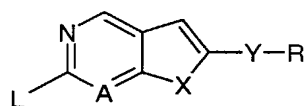
R^1 is hydrogen, R^2 is 4-tetrahydropyranyl, A is N, X is NR^3 , R^3 is methyl, Y is $C(=O)$, and R is 2-methoxyphenyl;

5 R^1 is hydrogen, R^2 is cyclopentyl, R' is hydrogen, A is N, X is NR^3 , R^3 is methyl, Y is CHR' , and R is phenyl;

R^1 is hydrogen, R^2 is 4-hydroxycyclohexyl, R' is hydrogen, A is NR^3 , X is N, R^3 is methyl, Y is CHR' , and R is phenyl; or

10 R^1 is hydrogen, R^2 is 4-tetrahydropyranyl, R' is hydrogen, A is N, X is NR^3 , R^3 is methyl, Y is CHR' , and R is phenyl.

36. A compound represented by Formula V:



Formula V

wherein:

A is N or CH;

X is O, NR^3 or S, wherein R^3 is hydrogen, alkyl or aryl; and

20 Y is a bond, O, NR' , $C(=O)$, $CH(OR')$, $CH(R')$, or $S(O)_n$, wherein n is 0, 1, or 2; and R' is hydrogen or alkyl;

R is aryl or heteroaryl; and

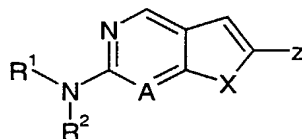
L is $R^a-S(O)_{n1}$, where R^a is alkyl or aryl and $n1$ is 0, 1 or 2.

37. The compound of Claim 36, wherein $n1$ is 2.

25

72

38. A compound of Formula VI



Formula VI

wherein:

A is N or CH;

R¹ is hydrogen, alkyl or arylalkyl;

R² is alkyl, hydroxyalkyl, heteroalkyl, (R'')₂NCO-alkylene- (where each R'' is independently hydrogen or alkyl), cycloalkyl, heterocyclyl, aryl, or heteroaryl;

X is O, NR³ or S, wherein R³ is hydrogen, alkyl or aryl; and

Z is hydrogen or halo.

39. The compound of Claim 37 or 38 wherein A is N and X is S.

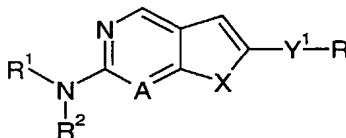
40. The compound of Claim 38, wherein:

R¹ is hydrogen; and

R² is alkyl, hydroxyalkyl, cycloalkyl, heterocyclyl or aryl.

41. A pharmaceutical composition comprising a therapeutically effective amount of one or more compound(s) according to any one of claims 1 to 35 in combination with a pharmaceutically acceptable carrier.

42. A process for producing a compound of the formula:



IA

wherein

A is N or CH;

R is aryl or heteroaryl;

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R^1 is hydrogen, alkyl or arylalkyl;

R^2 is alkyl, heteroalkyl, hydroxyalkyl, $(R'')_2\text{NCO-alkylene-}$ (where each R'' is independently hydrogen or alkyl), cycloalkyl, heterocyclyl, aryl, or heteroaryl;

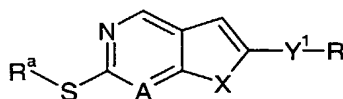
5 X is O, NR^3 or S, wherein R^3 is hydrogen, alkyl or aryl; and

Y^1 is C(=O) , CH(OR') , or CH(R') , wherein R' is hydrogen or alkyl,

said process comprising:

a) contacting a thioether of the formula:

10

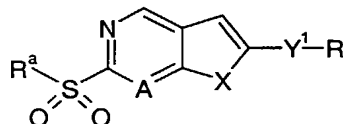


wherein

A, R, X and Y^1 are as defined above; and

R^a is alkyl or aryl,

15 with an oxidizing agent to produce an alkylsulfone compound of the formula:

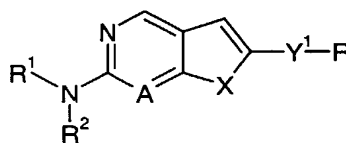


and

20 b) contacting the alkylsulfone compound with an amine compound of the formula NHR^1R^2 , wherein R^1 and R^2 are as defined above to produce the compound of Formula IB.

43. A process of producing a compound of Formula IB:

25



IB

wherein

A is N or CH;

R is aryl or heteroaryl;

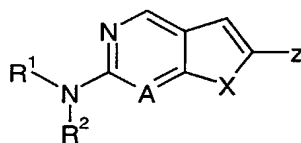
R¹ is hydrogen, alkyl or arylalkyl;

5 R² is alkyl, heteroalkyl, hydroxyalkyl, (R'')₂NCO-alkylene- (where each R'' is independently hydrogen or alkyl), cycloalkyl, heterocyclyl, aryl, or heteroaryl;

X is O, NR³ or S, wherein R³ is hydrogen, alkyl or aryl; and

Y¹ is O, NR', or S(O)_n, wherein n is 0, 1, or 2; and R' is hydrogen or alkyl;

10 said process comprising contacting a compound of the formula:



wherein

A, X, R¹ and R² are as defined above; and

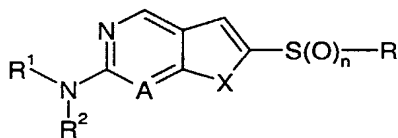
Z is halide,

15 with an aromatic or heteroaromatic compound of the formula HY¹-R, optionally in the presence of a base, to produce the compound of Formula IB, where Y¹ is O, NR', or S,

and when Y¹ is S, said process further comprising:

20 contacting the compound of Formula IB, where Y¹ is S with an oxidizing agent to produce the compound of Formula IB, where Y¹ is S(O)_n, where n is 1 or 2.

44. A process of producing a compound of Formula IC:



IC

25 wherein

n is 0, 1 or 2;

A is N or CH;

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R is aryl or heteroaryl;

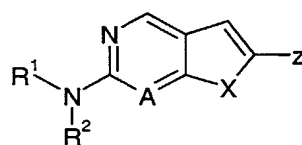
R¹ is hydrogen, alkyl or arylalkyl;

R² is alkyl, heteroalkyl, hydroxyalkyl, (R'')₂NCO-alkylene- (where each R'' is independently hydrogen or alkyl), cycloalkyl, heterocyclyl, aryl, or heteroaryl; and

X is O, NR³ or S, wherein R³ is hydrogen, alkyl or aryl;

said process comprising:

(a) contacting a compound of the formula:



wherein

R¹, R², A and X are as defined above; and

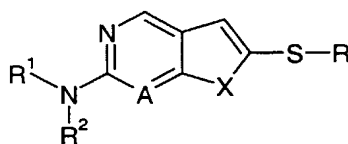
Z is halide,

with an organometallic reagent; and

(b) adding an aryl or heteroaryl disulfide of the formula:



to produce a thioether compound of the formula:



and when n is 1 or 2, said process further comprising:

(c) contacting the thioether compound with an oxidizing agent to produce the compound of Formula IC where n is 1 or 2.

45. A process as claimed in any one of claims 42 to 44 wherein X is methyl or phenyl and R² is not heteroalkyl.

46. A compounds as claimed in any one of claims 1 to 35 whenever prepared by a process as claimed in any one of claims 42 to 44.

47. A method for treating a p38 protein kinase mediated disorder comprising administering to a patient in need of such treatment, an effective amount of a compound according to any one of claims 1 to 35.

5 48. The method of claim 47, wherein the p38 protein kinase mediated disorder is selected from the group consisting of arthritis, Crohn's disease, Alzheimer's disease, irritable bowel syndrome, adult respiratory distress syndrome, and chronic obstructive pulmonary disease.

10 49. Use of a compound as claimed in any one of claims 1 to 35 for the preparation of a medicament for the treatment of a p38 protein kinase mediated disorder.

15 50. The use of claim 49, wherein the p38 protein kinase mediated disorder is selected from the group consisting of arthritis, Crohn's disease, Alzheimer's disease, irritable bowel syndrome, adult respiratory distress syndrome, and chronic obstructive pulmonary disease.

20 51. The invention as hereinbefore described.

INTERNATIONAL SEARCH REPORT

Internati Application No

PCT/EP 03/02090

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D495/04 C07D487/04 C07D491/04 A61K31/519 A61P19/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02 14317 A (ORTHO MCNEIL PHARM INC) 21 February 2002 (2002-02-21) example 8B	38
A	--- WO 99 20624 A (HOFFMANN LA ROCHE) 29 April 1999 (1999-04-29) claims example 3	1, 36, 38, 41, 47, 49
A	--- WO 98 06715 A (RAHMAN SHIRLEY K ; SMITHKLINE BEECHAM PLC (GB); ADAMS JERRY LEROY ()) 19 February 1998 (1998-02-19) claims -----	1, 36, 38, 41, 47, 49

☐

Further documents are listed in the continuation of box C.

☒

Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

8 July 2003

Date of mailing of the international search report

18/07/2003

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Authorized officer

Diederer, J

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/02090**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 47-48 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

 Internal Application No
 PCT/EP 03/02090

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0214317	A	21-02-2002	US 2002040019 A1	04-04-2002
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			WO 9806715 A1	19-02-1998